NET and GIST

Molecular and Ancillary Studies

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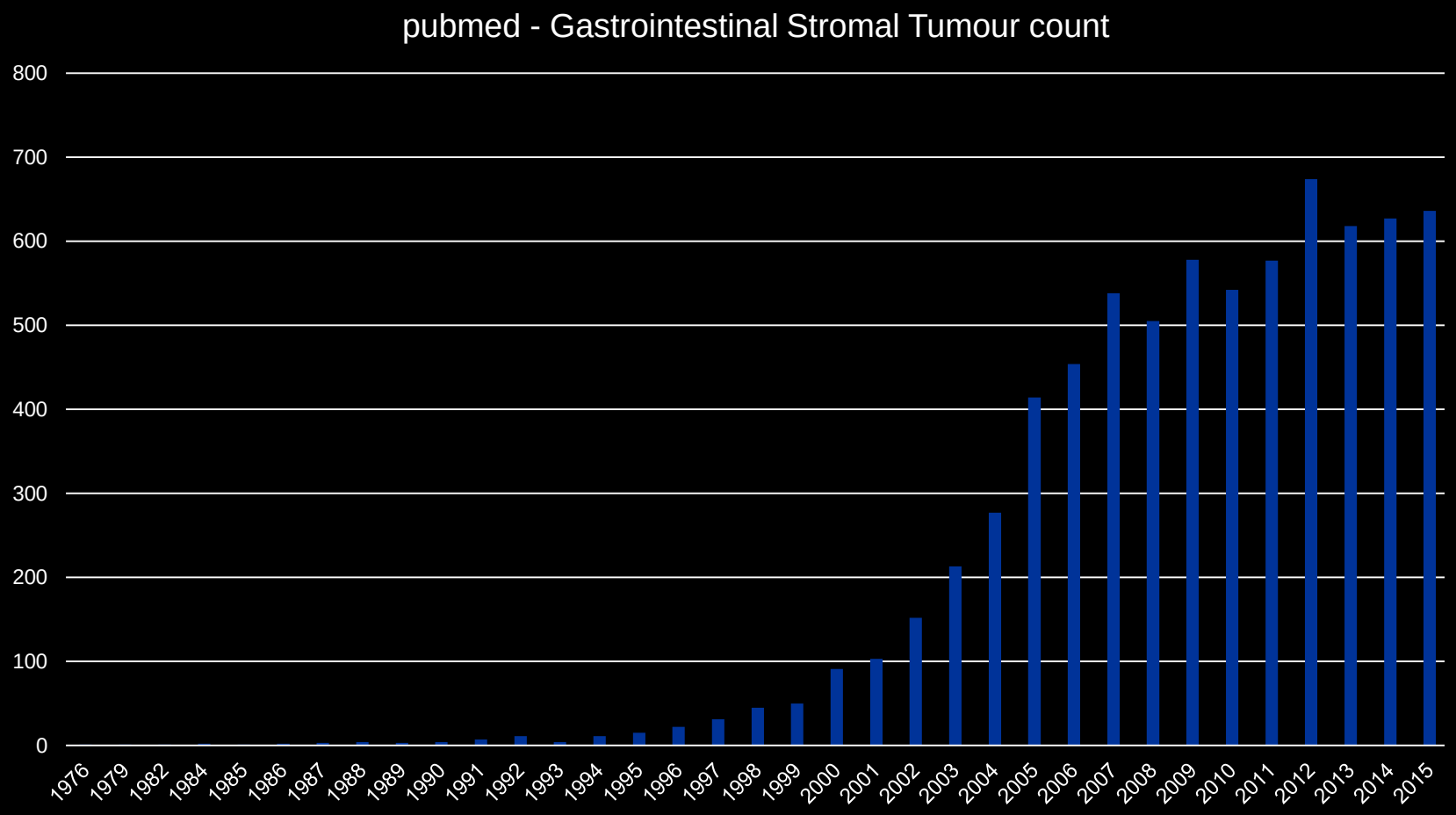
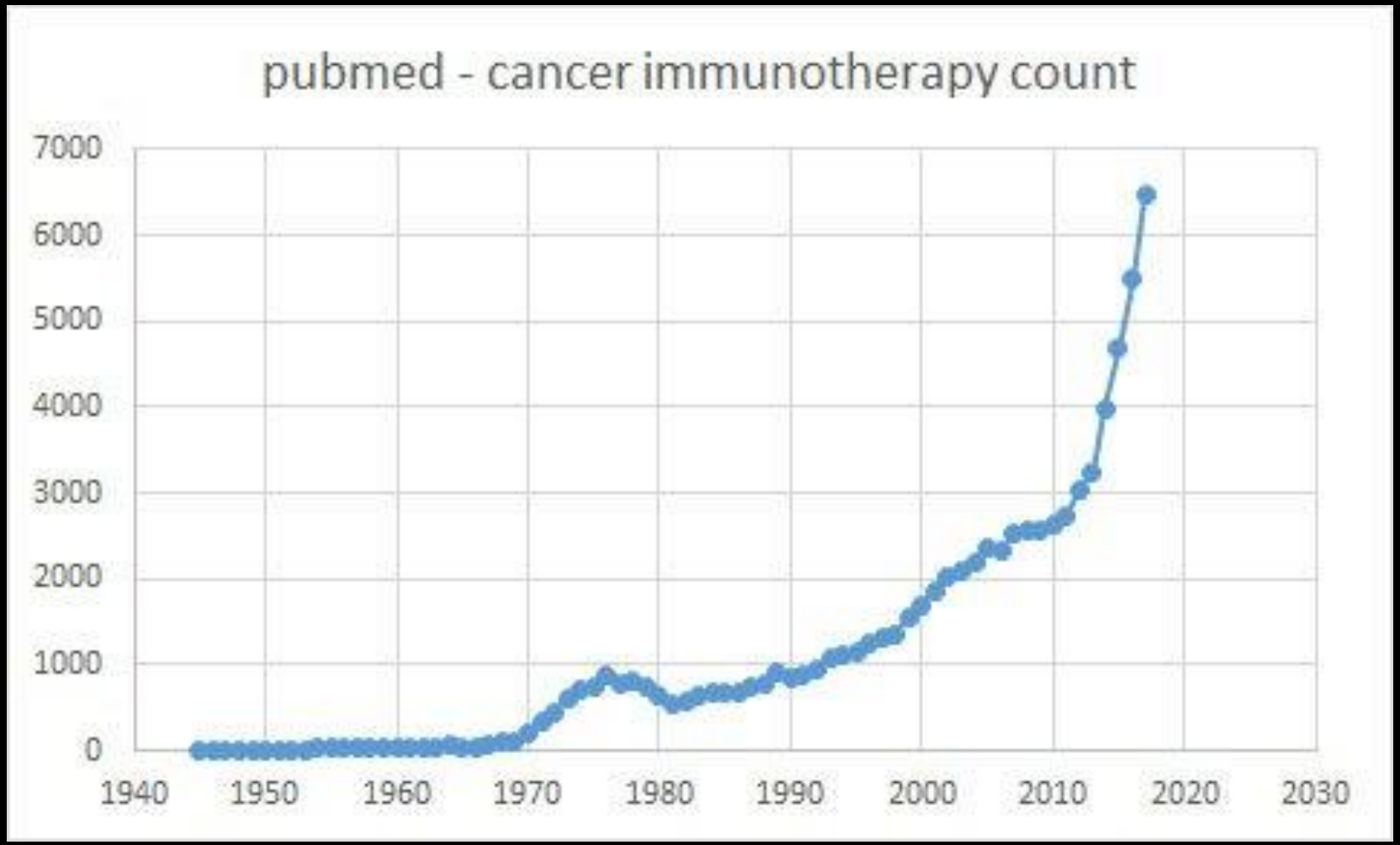
Dr Gill has no conflicts of interest to disclose

PUBMED Search
“Gastrointestinal Stromal Tumour”
1976 - 2015

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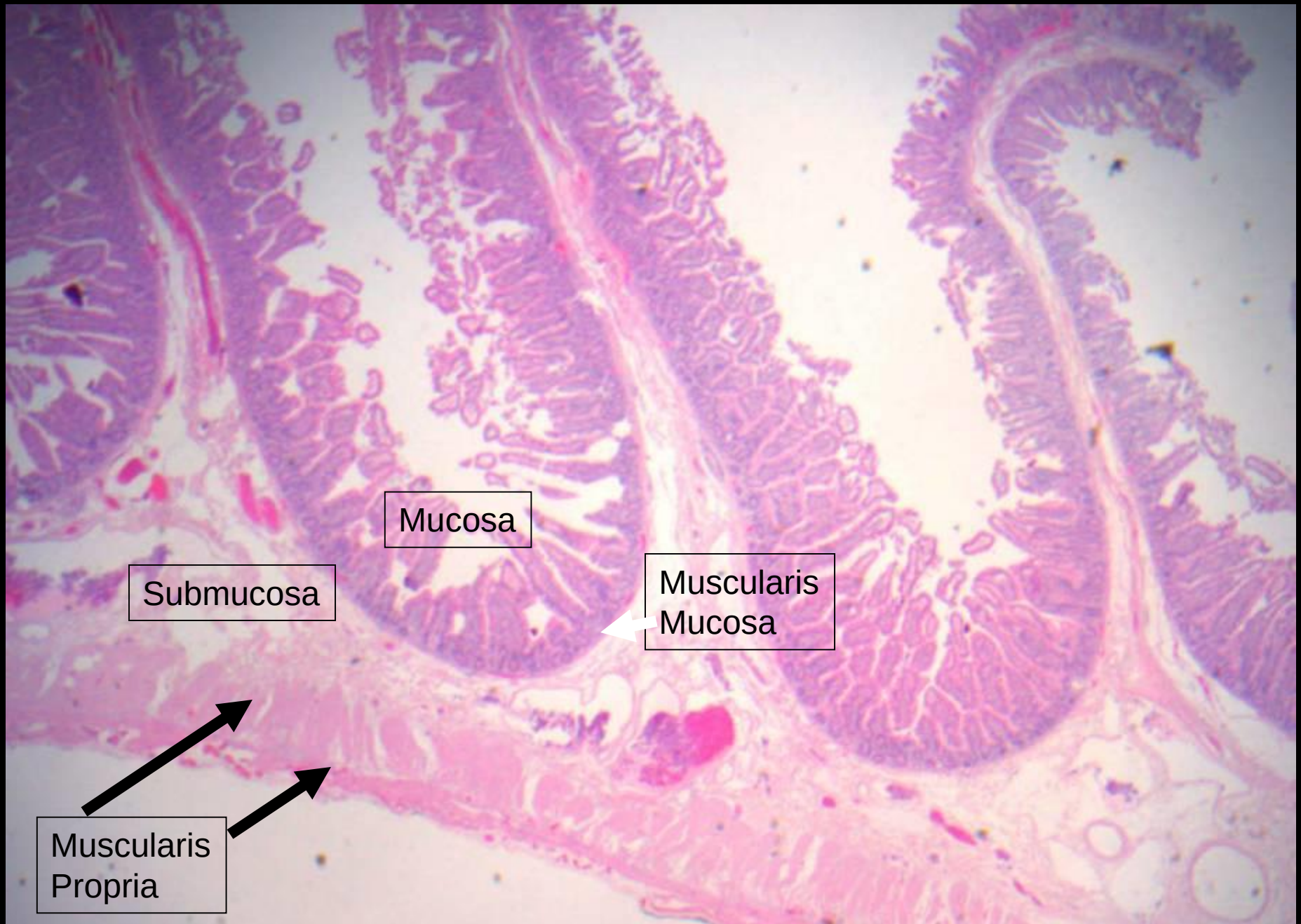
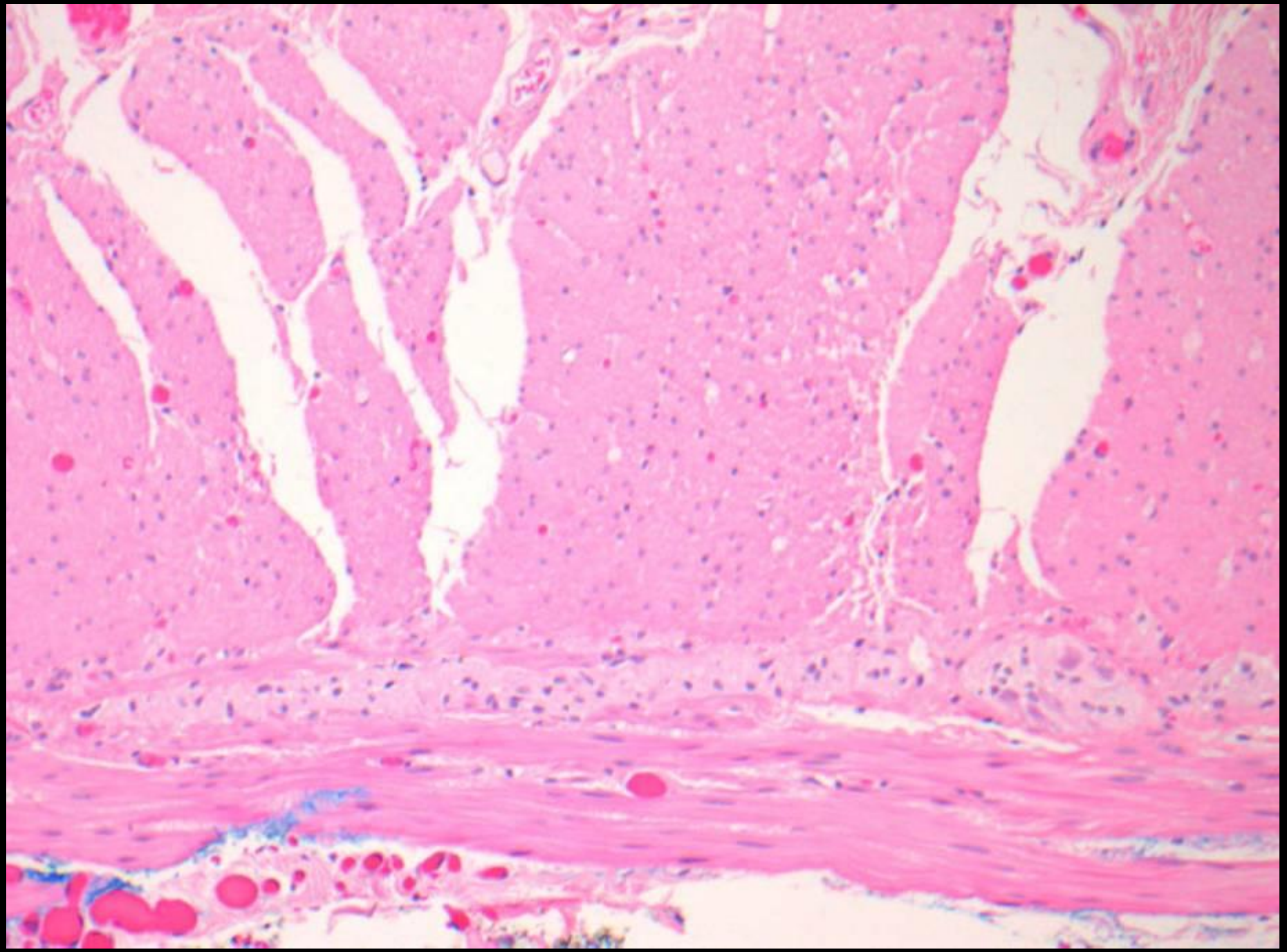
Gastrointestinal stromal tumour GIST

- Paradigm for classification (morphology and molecular)
- Paradigm for targetted therapy and personalised medicine
- Paradigm for predictive molecular pathology

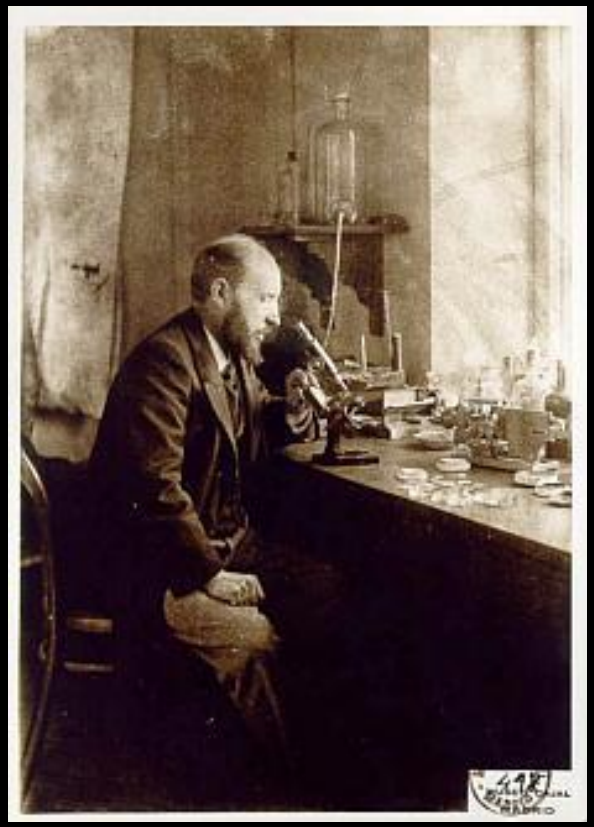
NORMAL SMALL INTESTINE





INTERSTITIAL PACEMAKER CELLS OF CAJAL

Santiago Ramón y Cajal (1852 -1934)



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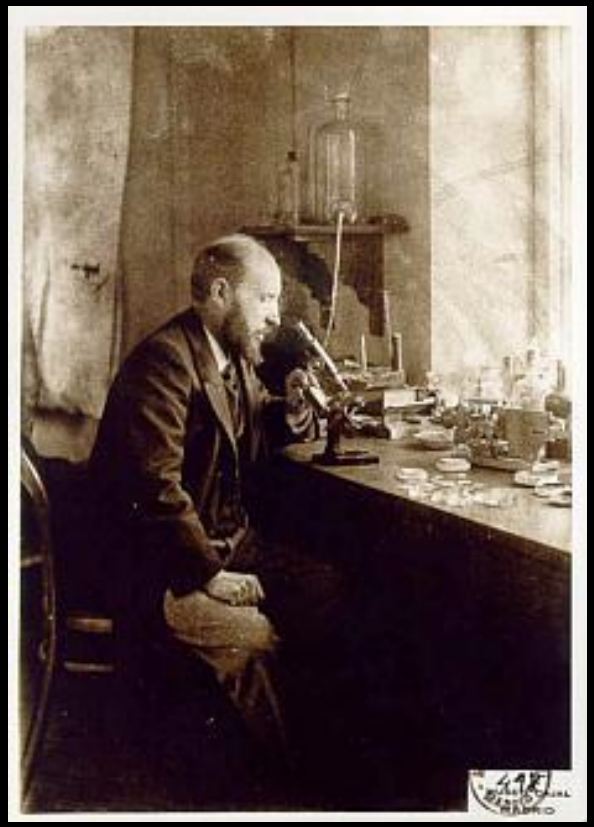


He was an avid painter, artist, and gymnast. He worked for a time as a shoemaker and barber, and was well known for his pugnacious attitude.

In 1905, he published five science-fictional "Vacation Stories" under the pen name "Dr. Bacteria.“

Shared Nobel prize 1906:

“*in recognition of their work on the structure of the nervous system*”

Gastrointestinal stromal tumour GIST

- 4500 – 10000 cases pa in USA
  - (300-450 cases in Australia)
- 0.2% of all GIT tumours
- 80% of GIT sarcomas
- Most common sarcoma
- Incidence Male=Female
- Most common 40 to 60 years
- 6cm Stomach; 4.5cm Duodenum; 7cm ileum

Gastrointestinal stromal tumours

- 5% Oesophagus (2% at RNSH)
- 50% Stomach (56% at RNSH)
- 33% Small bowel (28% at RNSH)
- 10% colon/rectum/anus (8% at RNSH)
- 2% EGIST (7% at RNSH)

  (outside the tubal gut – omentum or mesentery near stomach – appear to be gastric GISTs)

Risk stratification by size and mitotic rate in GIST

TABLE 2. Proposed Approach for Defining Risk of Aggressive Behavior in GISTs

	Size*	Mitotic Count†
Very low risk	<2 cm	<5/50 HPF
Low risk	2–5 cm	<5/50 HPF
Intermediate risk	<5 cm	6–10/50 HPF
	5–10 cm	<5/50 HPF
High risk	>5 cm	>5/50 HPF
	>10 cm	Any mitotic rate
	Any size	>10/50 HPF

Note: These are “conventional” high powered fields. Now most surgical pathologists use wide field microscopics

Risk stratification by size and mitotic rate in GIST

Prognostic Group and Definition	Patients With Metastases of All in the Group (%)	
	Children and Young Adults	All Gastric GIST Patients
2 (≤5 cm, ≤5/50 HPF)	1/6 (17%)	6/320 (2%)
3A (5 ≤ 10 cm, ≤5/50 HPF)	2/7 (28%)	8/229 (3%)
3B (>10 cm, ≤5/50 HPF)	1/2 (50%)	17/140 (12%)
5 (>2 ≤ 5 cm, >5/50 HPF)	1/7 (14%)	16/99 (16%)
6A (>5 ≤ 10 cm, >5/50 HPF)	3/5 (60%)	52/96 (54%)
6B (>10 cm, >5/50 HPF)	2/3 (67%)	89/108 (82%)

Note: Only cases with follow-up and defined tumor size are included.

IHC staining in GISTs

95% are cKIT positive
95% are DOG1 (Ano1) positive

Essentially all GISTs are positive for either cKIT or DOG1

70% CD34 positive
40% SMA positive
5% S100 positive
1% Keratin/Desmin positive

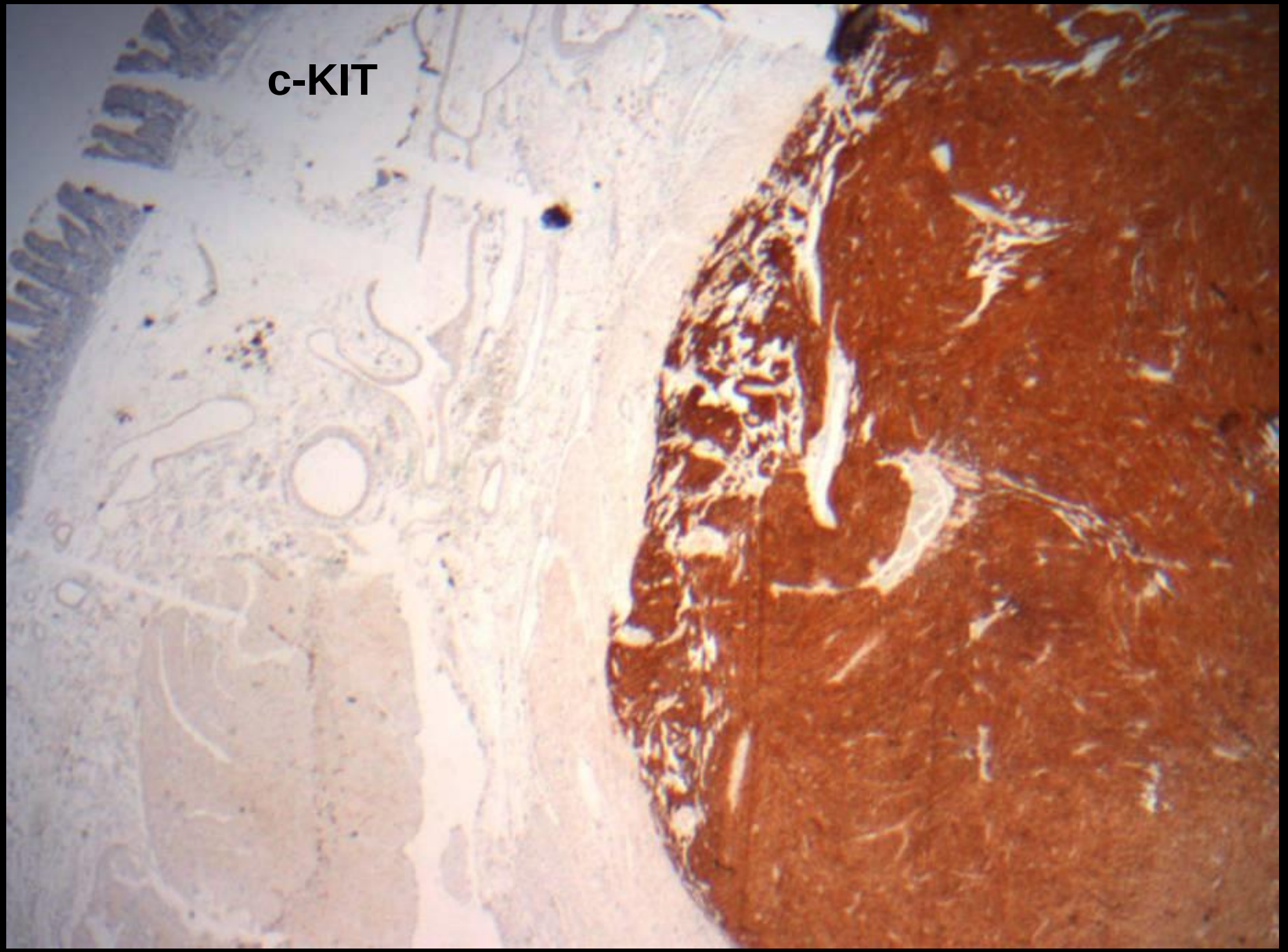
DOG1 better for gastric, epithelioid, PDGFRA

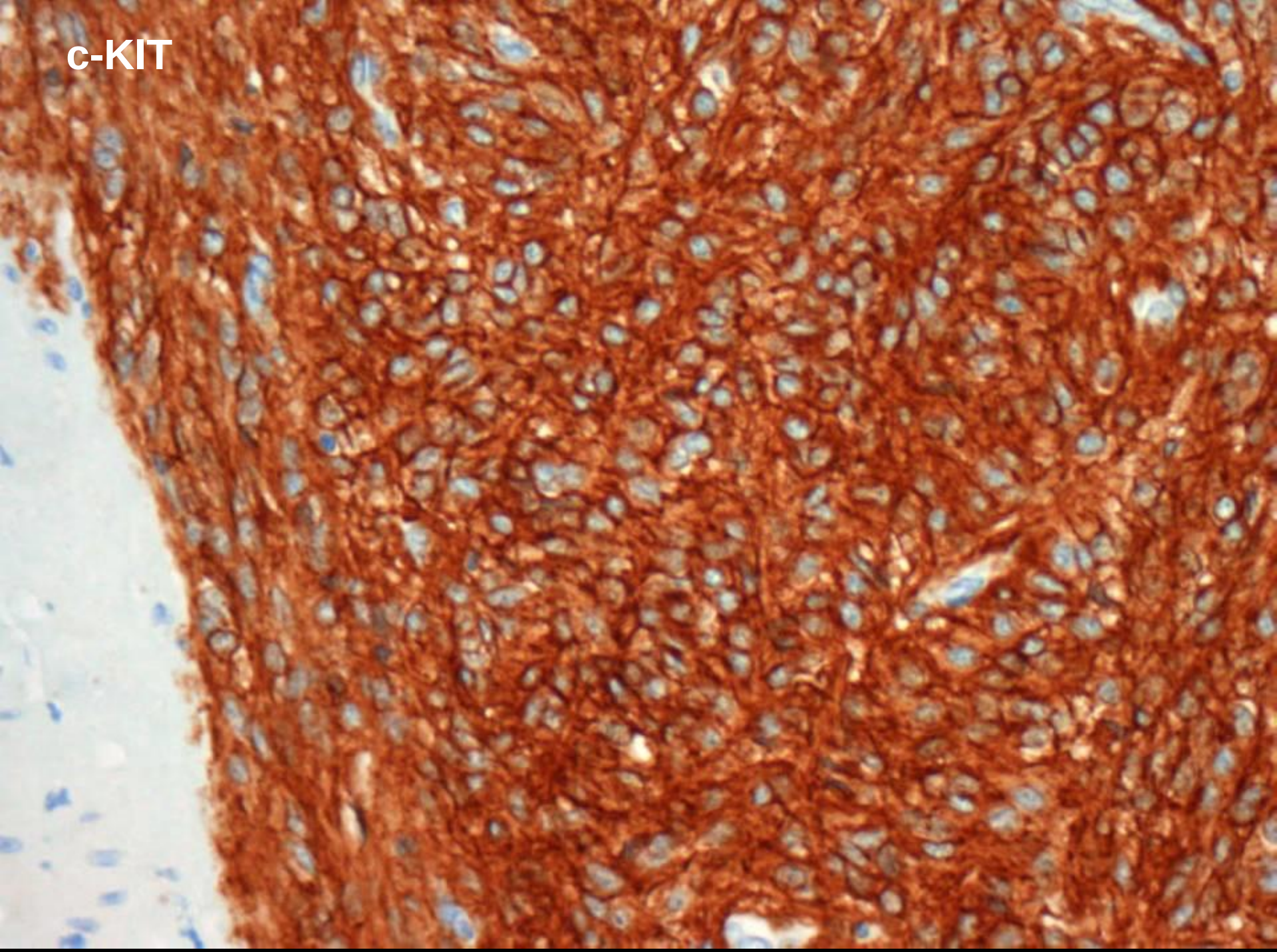
cKIT IHC negative GISTs comprise 5% of GISTS

(‘always’ DOG1 positive)

72% PDGFRA mutated
66% epithelioid
56% gastric
39% EGIST (ie: probably also GASTRIC)

ref: Medeiros F, Corless CL, Duensing A et al KIT negative Gastrointestinal Stromal Tumours: Proof of concept and therapeutic implictaions Am J Surg Pathol 2004;28:889–894


c-KIT


c-KIT

PDGFRA mutant GISTs

5-10% of all GISTs

Mostly gastric (and E-GIT) location

Epithelioid

Giant cells

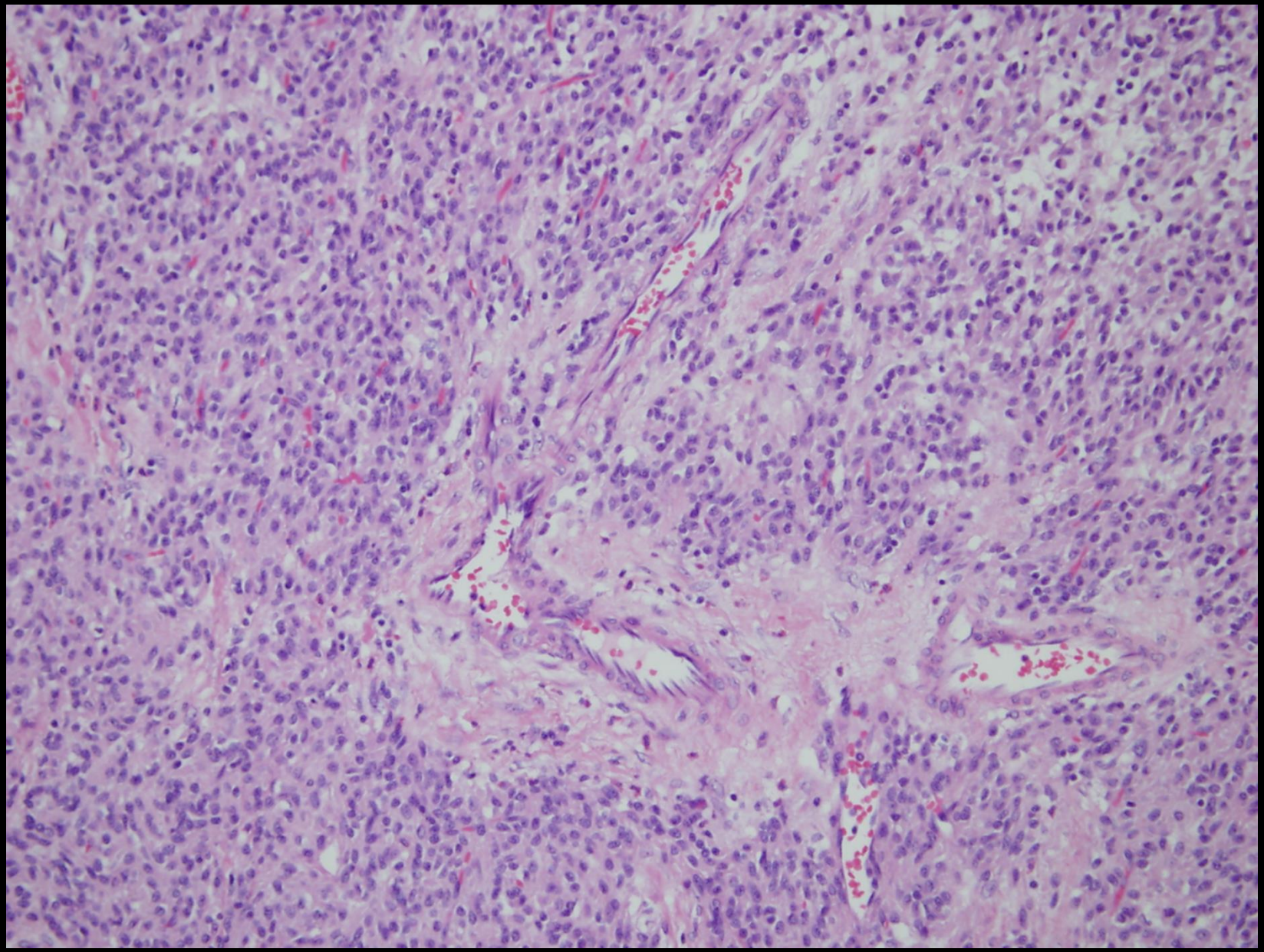
Myxoid stroma

Multinucleate cells

Rhabdoid morphology

Commonly KIT IHC neg/focal but DOG1 pos

Better prognosis than KIT negative GISTs



PDGFRA mutant GIST – Gastric location, epithelioid morphology, often with scattered multinucleate or bizarre cells, DOG1 positive, CKIT negative or focal

Molecular pathogenesis of GIST

Prior to 2010
Molecular pathogenesis of GIST

- 80-85% of GISTS have mutations of c-kit
- 5-10% have mutations of PDGFRalpha

- 10-15% have no mutations – no mutations in KIT and PDGFRalpha (previously known as wild type GISTs)

Wild-Type GIST meant no mutation in c-KIT or PDGFRalpha

October 2018
Molecular pathology of GISTs

KIT mutation 80-85%

PDGFRA mutation 5-10%

SDH Deficient (3% = 5 to 7.5% of Gastric GISTs)

BRAFV600E mutant 1%

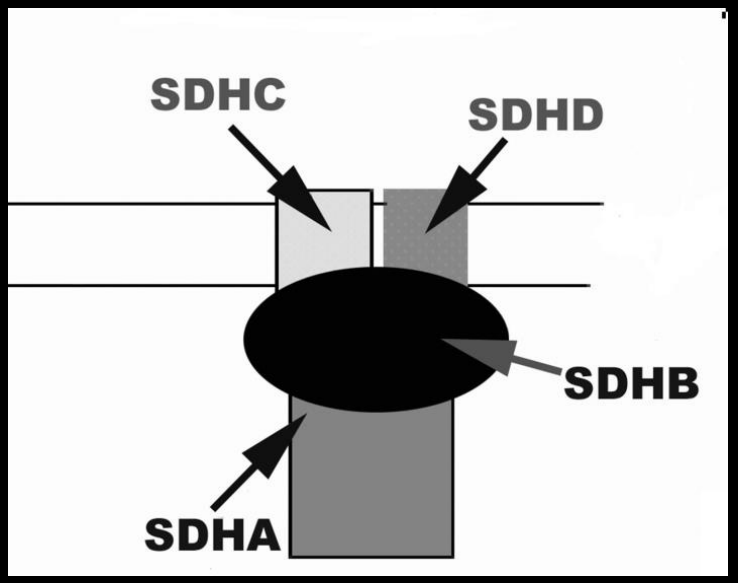
NF1 mutant 1%

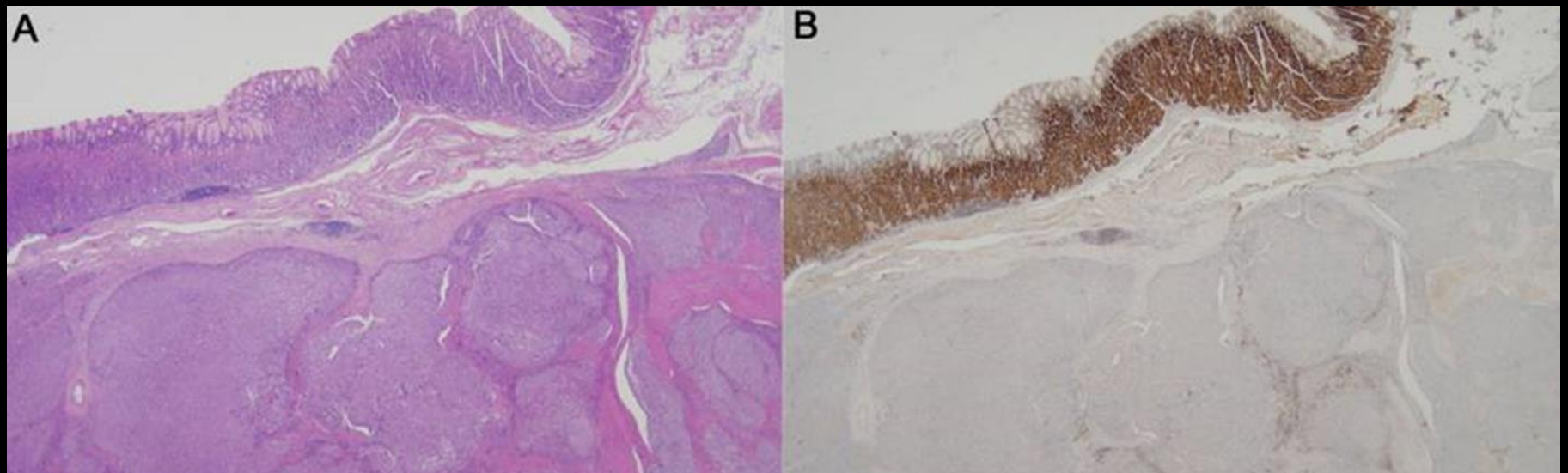
KRAS/NRAS <1%

. . . getting close to 100% of GISTs with known mutations. . .

Now if there is a true wild type GISTs the diagnosis should be questioned

SDH deficient GIST





Succinate Dehydrogenase Deficient GISTs

Only occur in the stomach*

Accounts for 5 to 7.5% of apparently sporadic gastric GISTs (great majority of pediatric GISTs)

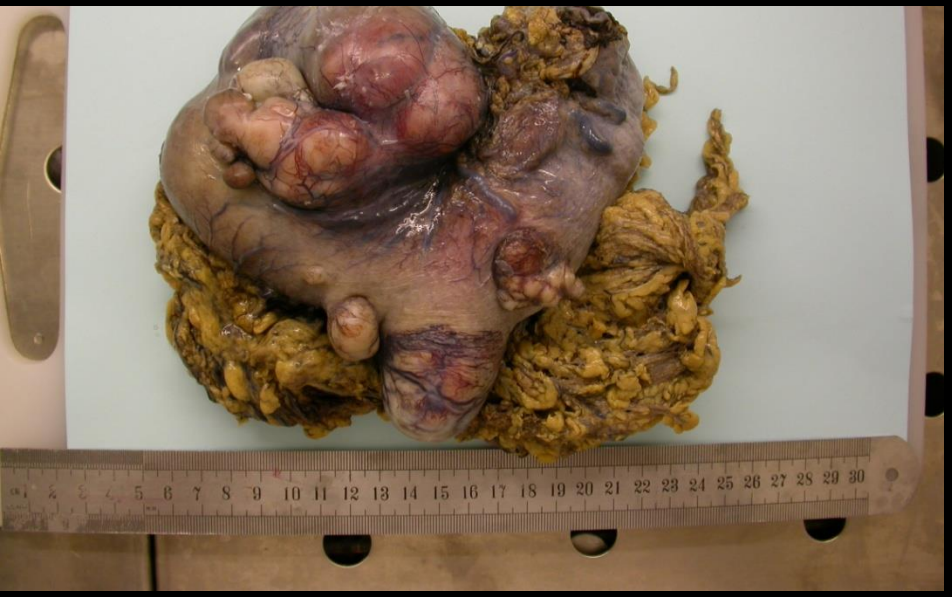
Demonstrate distinctive morphological and clinical features

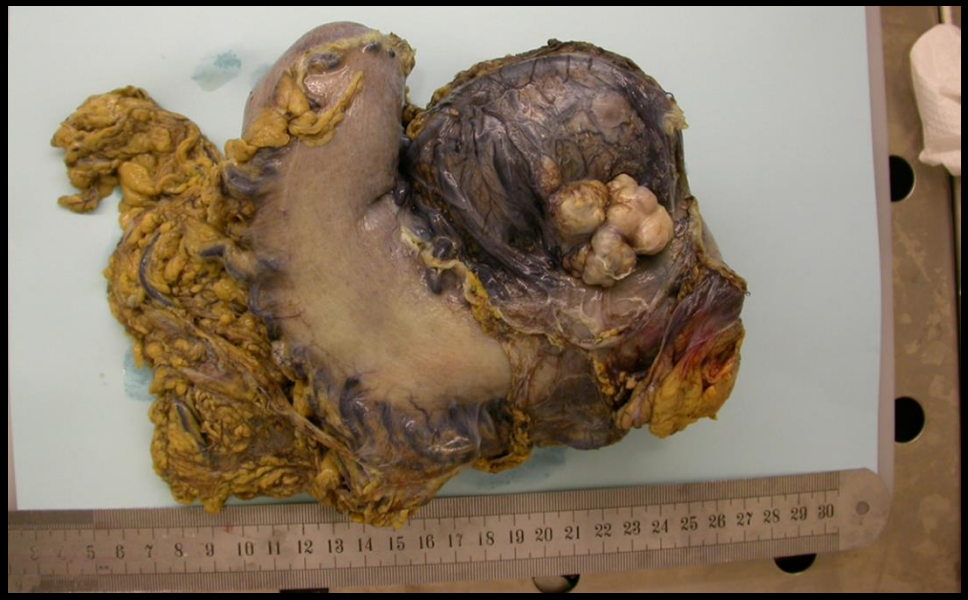
Identified by morphology in conjunction with immunohistochemistry for SDHB

* One exception -

Elston M, et al *A Duodenal SDH-Deficient Gastrointestinal Stromal Tumor in a Patient With a Germline SDHB Mutation* J Clin Endocrinol Metab. 2017;102:1447-1450

Succinate Dehydrogenase deficient GIST





SDH deficient GISTs are commonly multifocal
SDH deficient GISTs only occur in the stomach

Succinate Dehydrogenase deficient GIST

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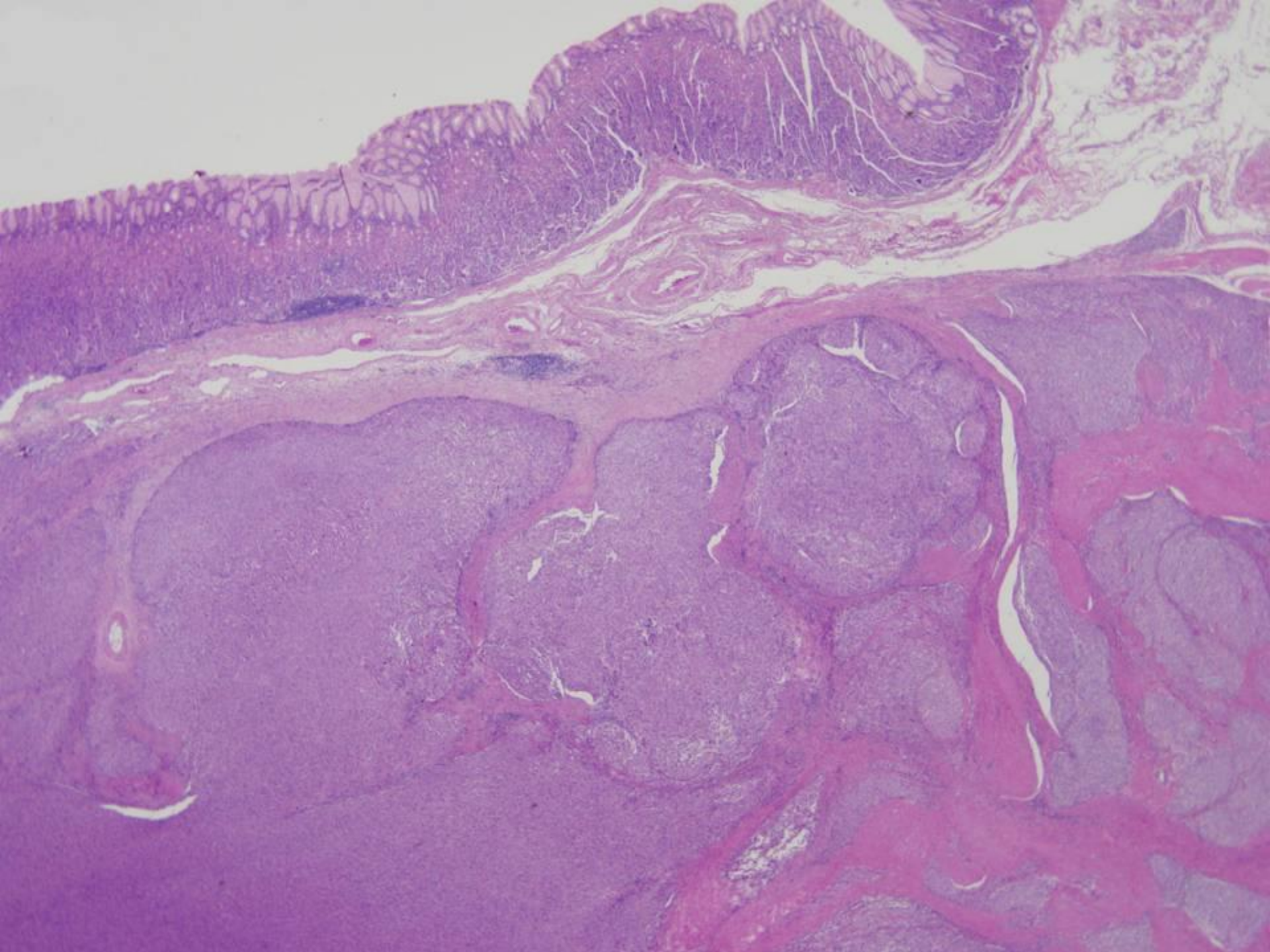
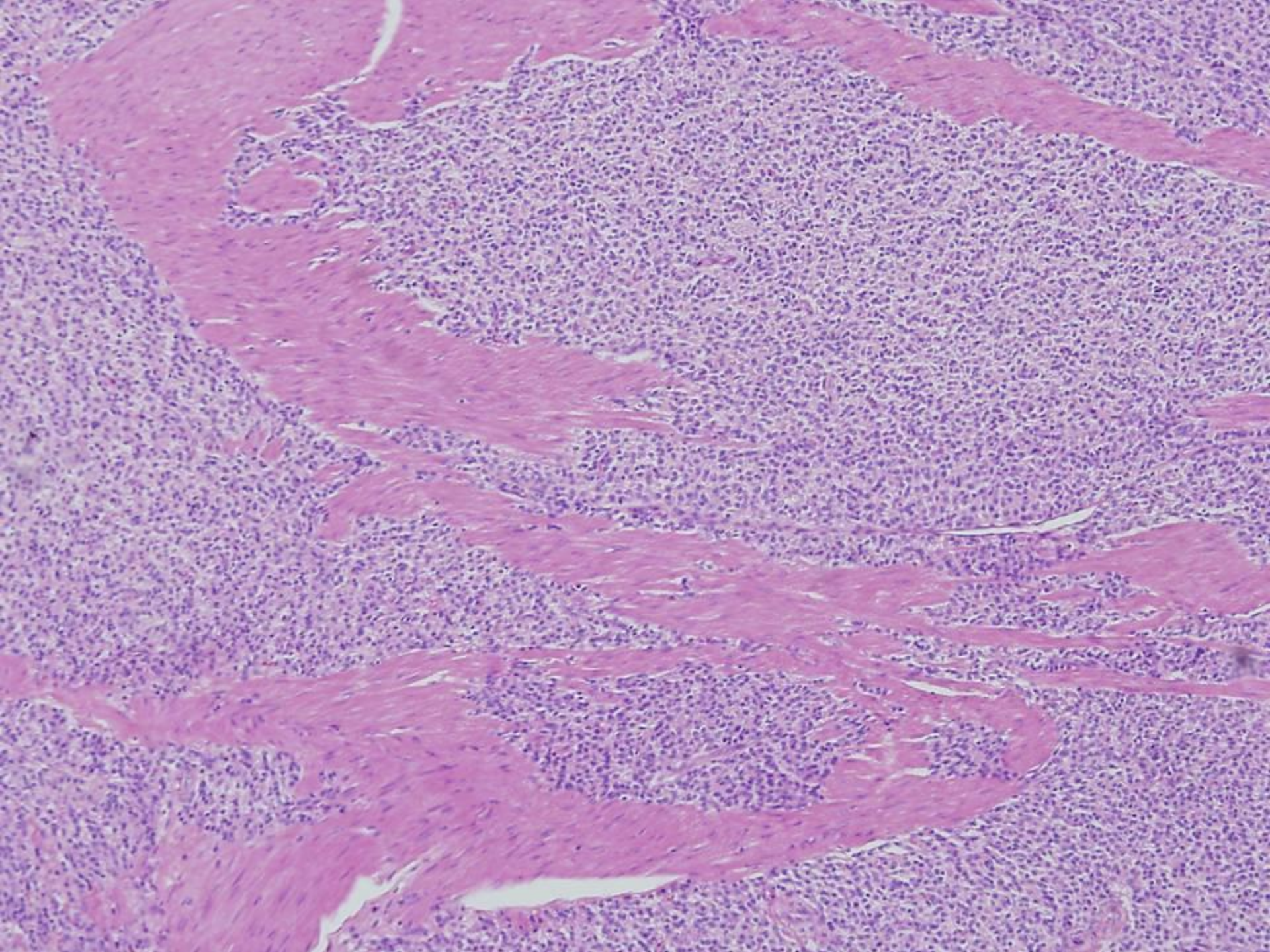
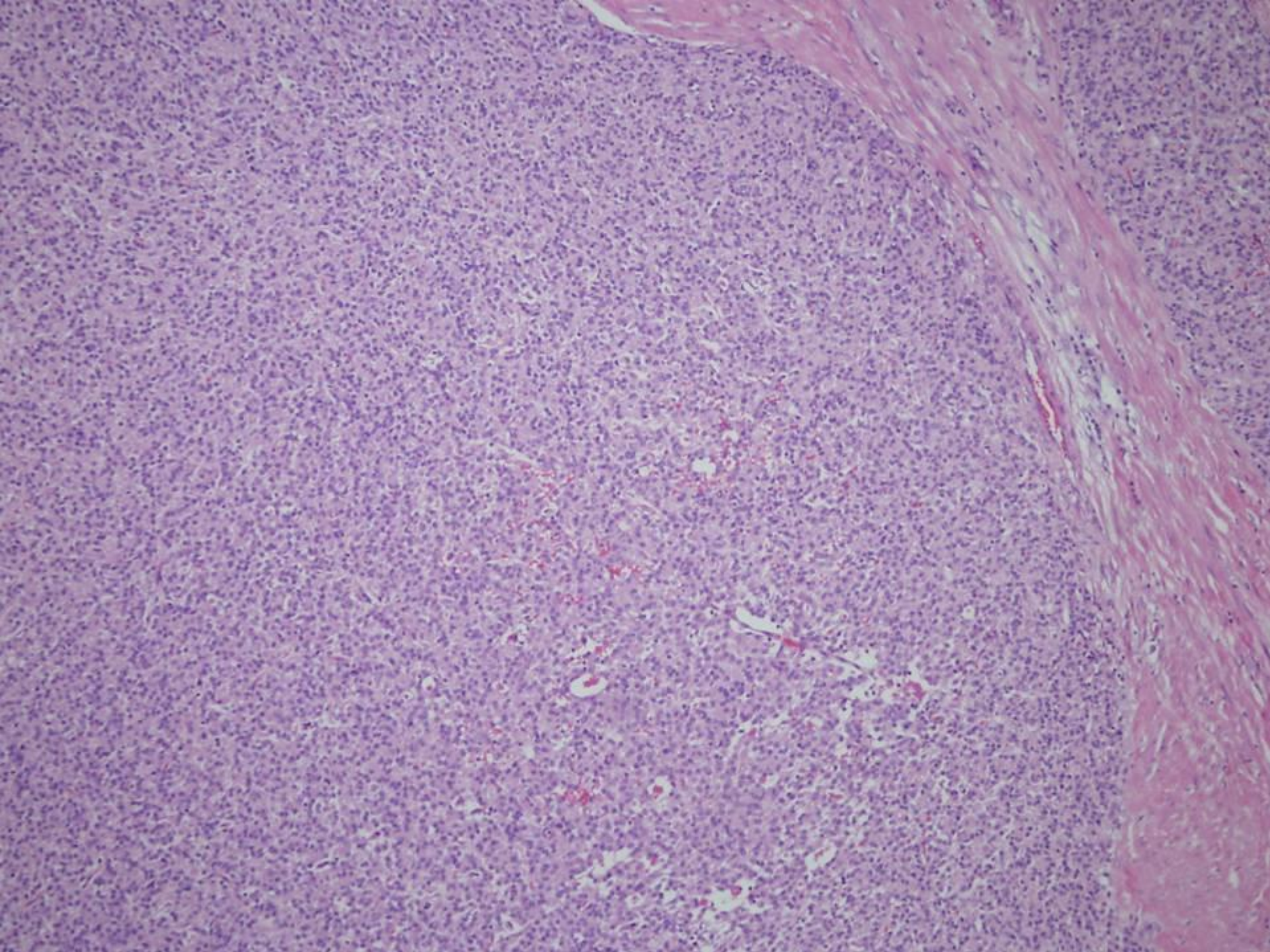
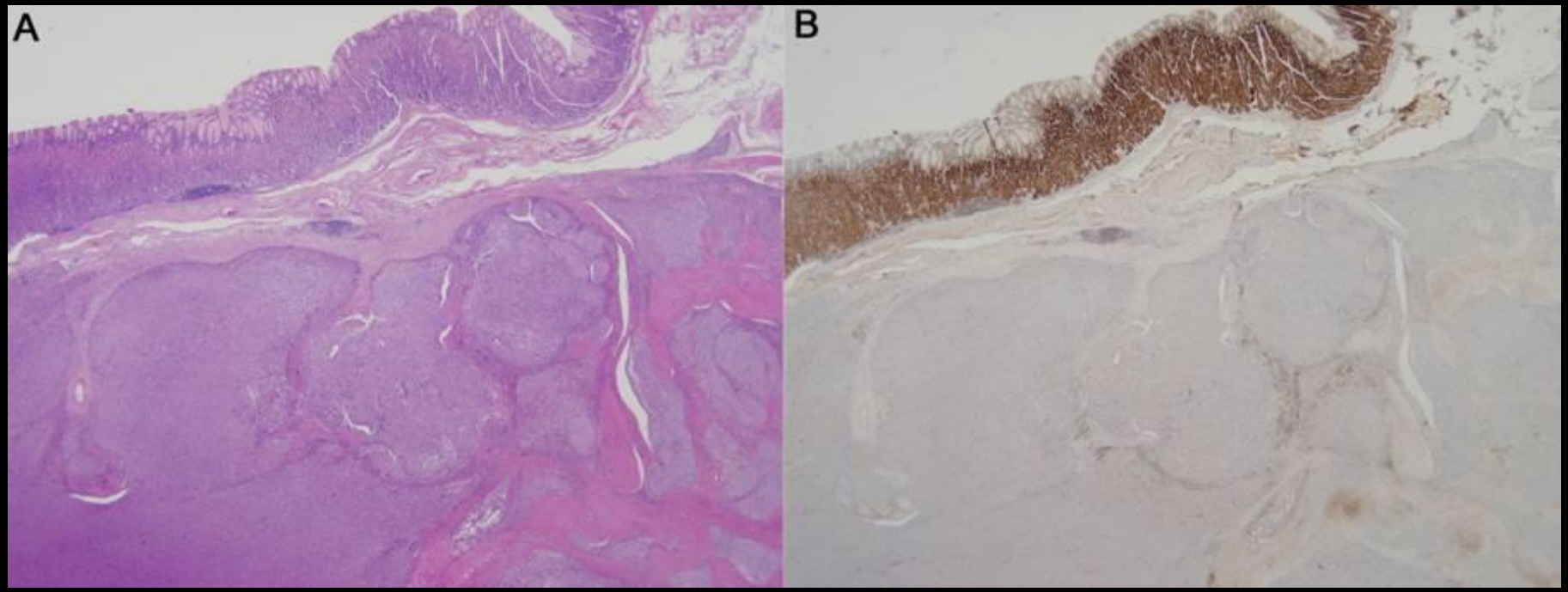






SDH deficient GISTs with negative SDHB IHC



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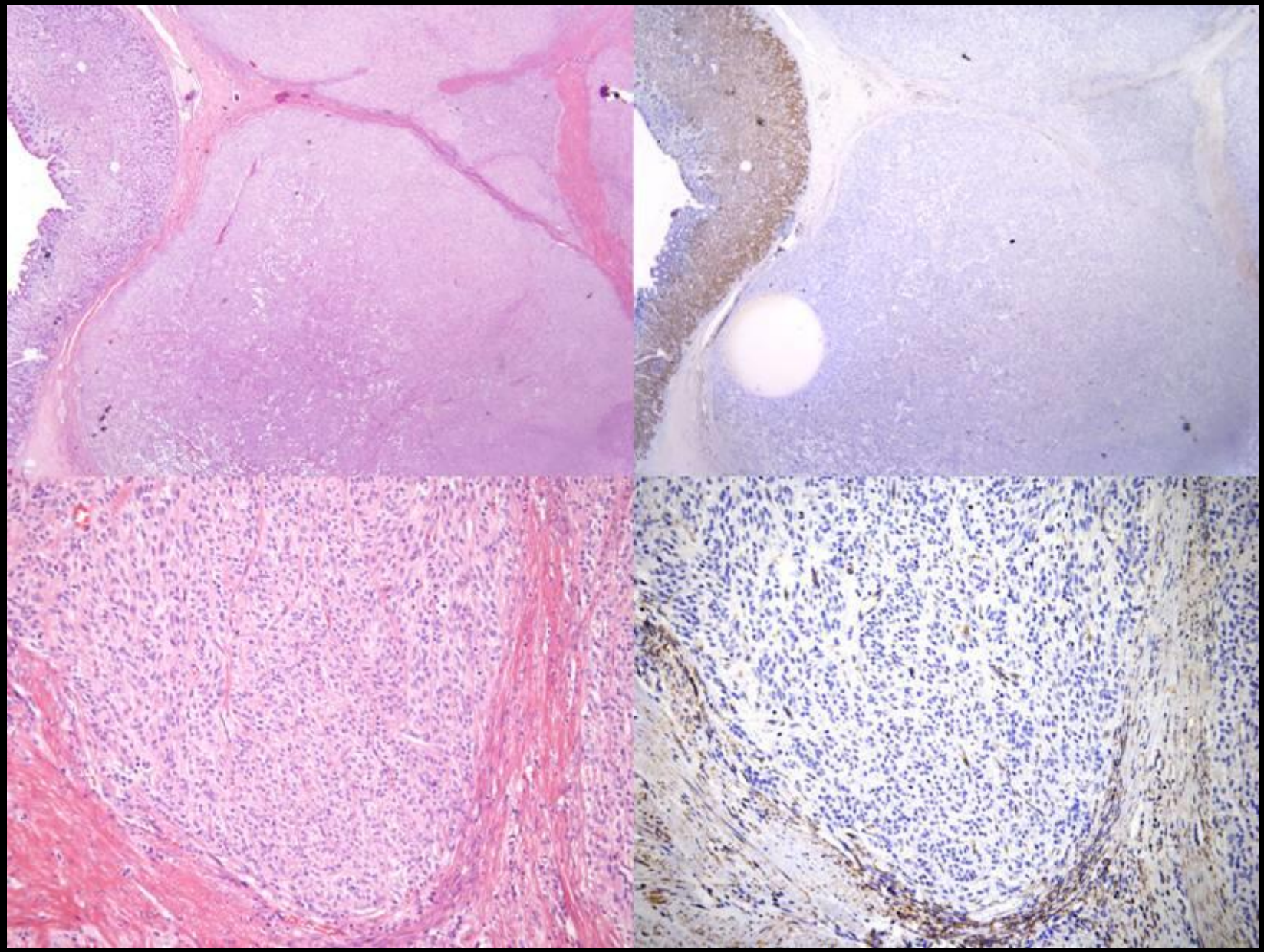
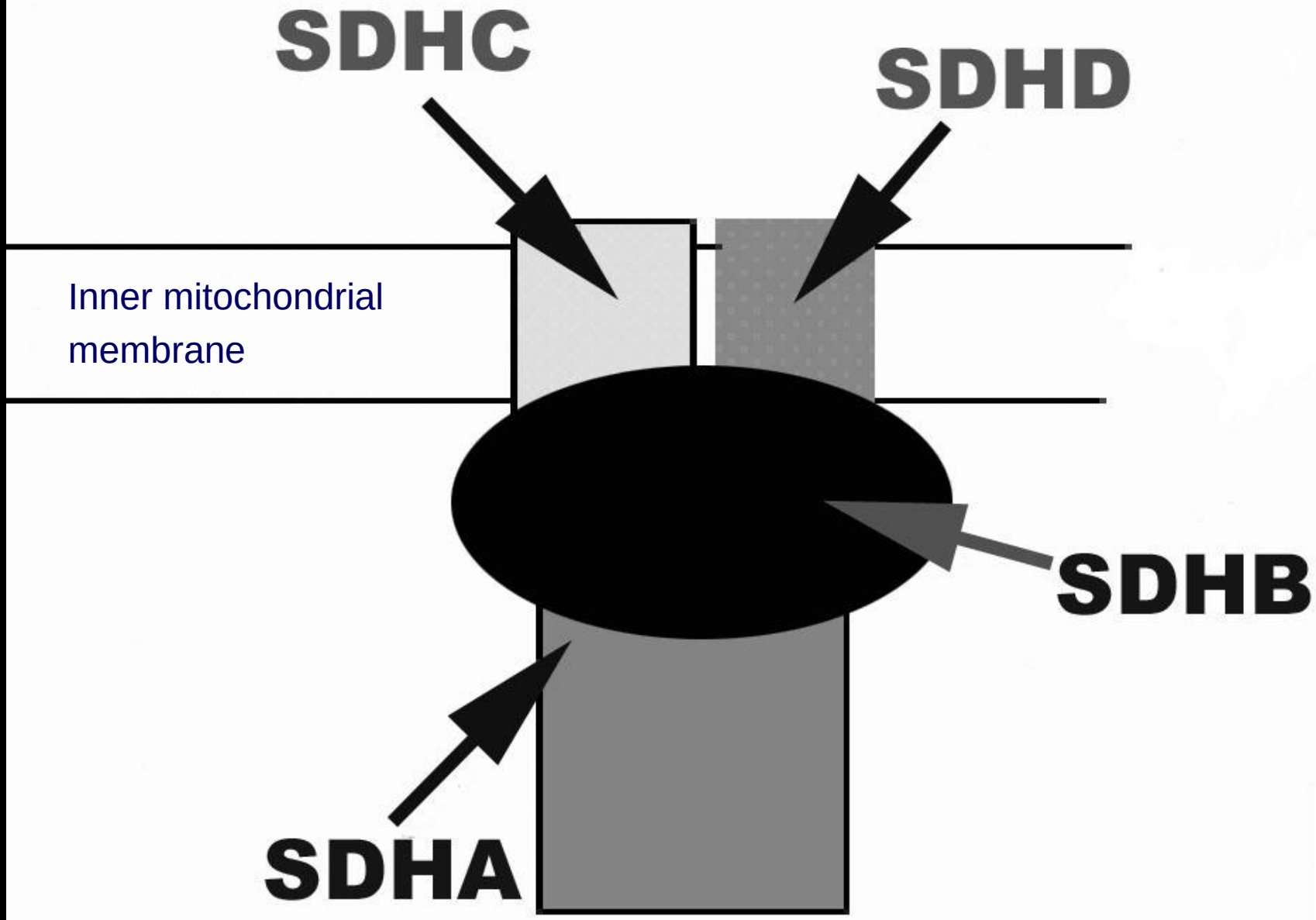
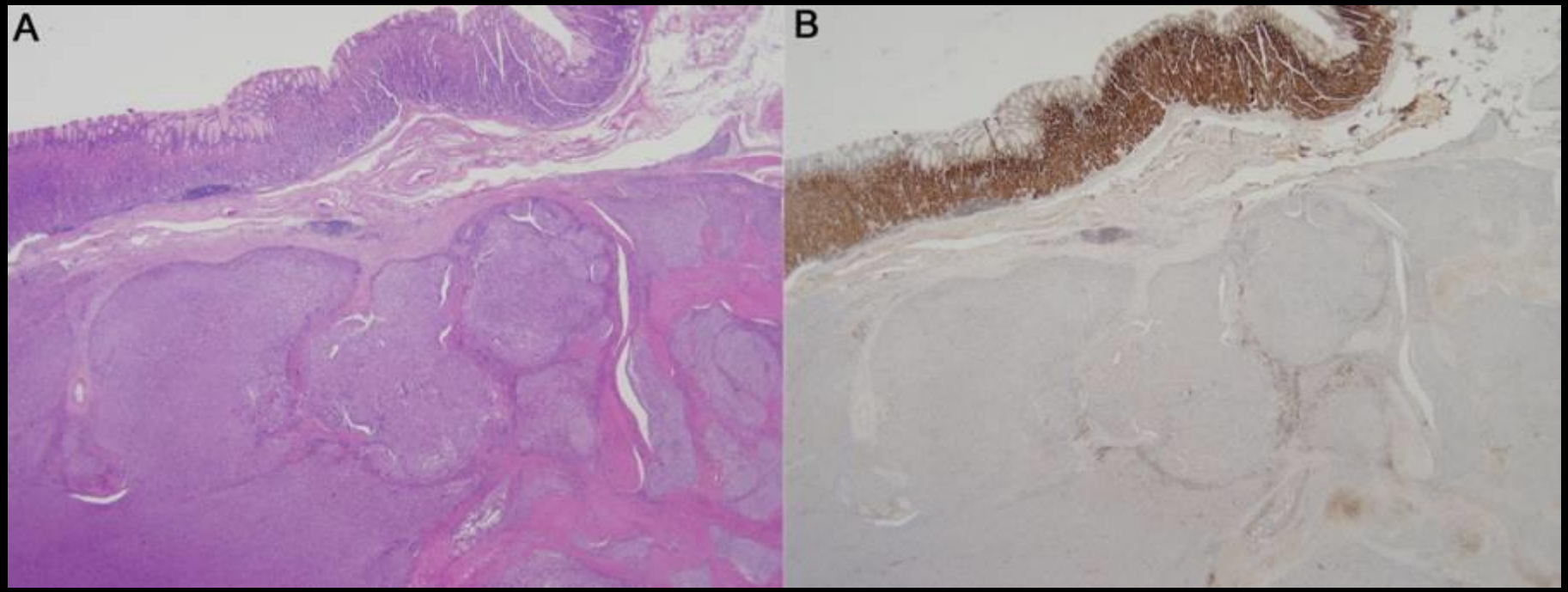


MITOCHONDRIAL COMPLEX 2



SDH deficient GISTs with negative SDHB IHC



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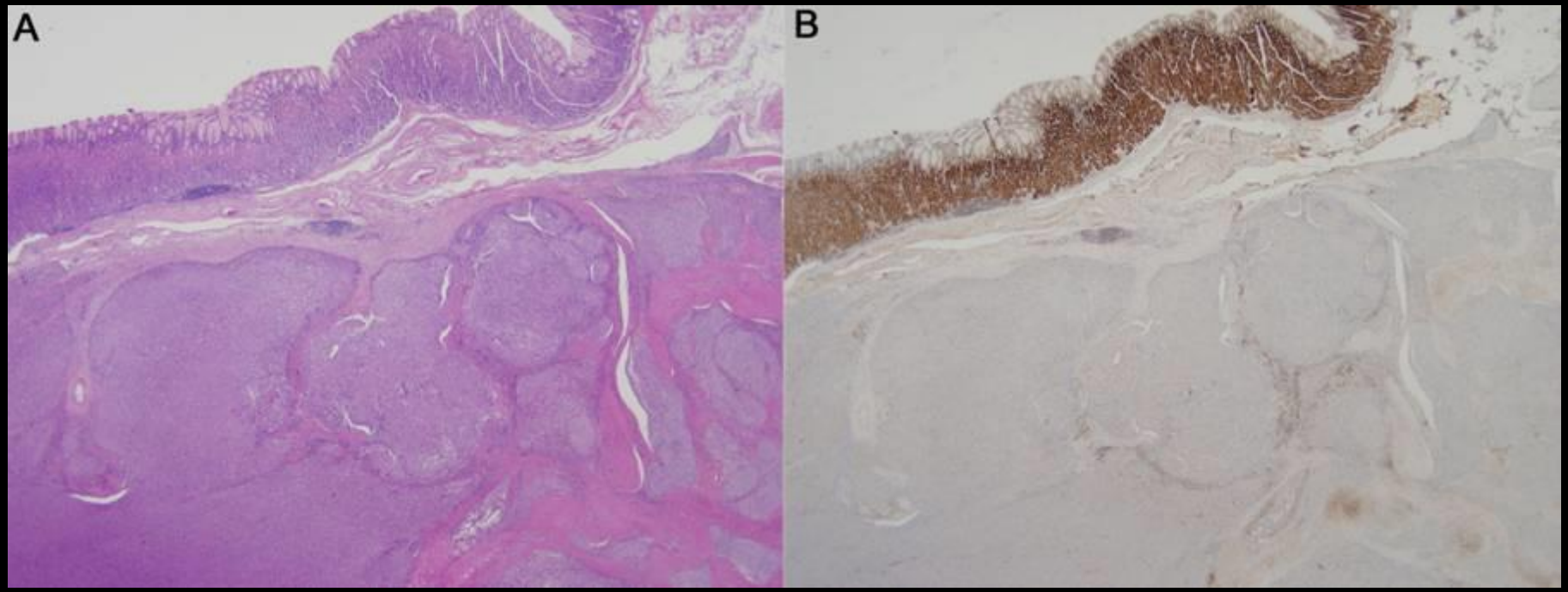
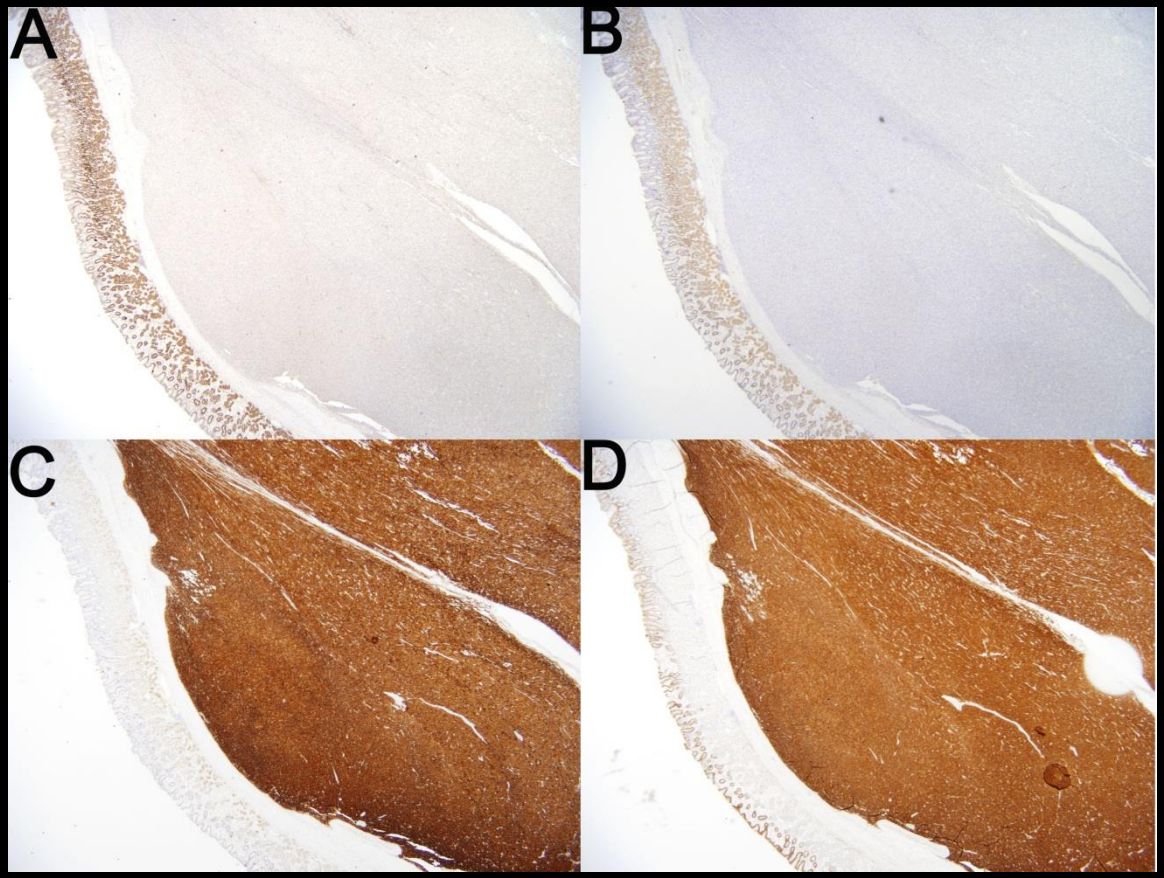


SDH deficient GISTs are always diffusely strongly cKIT and DOG1 positive

All succinate dehydrogenase deficient GISTs are syndromal

- 30% will be associated with germline SDHA mutation
- 10 to 20% will be associated with germline SDHB, C or D mutation
- All the rest will have SDHC promoter hypermethylation - that is, they probably have Carney Triad

30% of SDH deficient GISTs are SDHA mutated (germline)



SDHB

SDHA

cKIT

DOG1

SDHA mutant GISTs also show negative staining for SDHA

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SDH deficient GISTs are quite different to usual (KIT/PDGFRa mutated) GISTs

Table 2. Comparison of SDH-deficient and usual GISTs

	Usual GIST	SDH-deficient GIST
SDHB IHC	Positive	Negative
Somatic KIT/PDGFRA mutation	Usually	Never
KIT/DOG1 IHC	Usually positive	Always positive
Location	Throughout GIT	Stomach only*
Prognosis predicted by size and mitotic rate algorithm	Yes	No
Gender	Male–female	Female>>>male
Multi-focality	Rare	Common
Age	Older adult	Children>>>young adult>>older adult
Multi-nodularity/lobulation	Rare	Common
Predominant cell type	Spindled	Epithelioid
Lymph node metastasis	Very rare (if at all)	Common
Response to imatinib	Usual	Never
Behaviour of metastasis	Aggressive	Commonly indolent
Associated syndromes	Rare Neurofibromatosis Germline KIT mutation Germline PDGFRA mutation	Always ??? 30% germline SDHA mutation 50% SDHC epimutation (Carney triad) 20% SDHB, SDHC, SDHD mutation

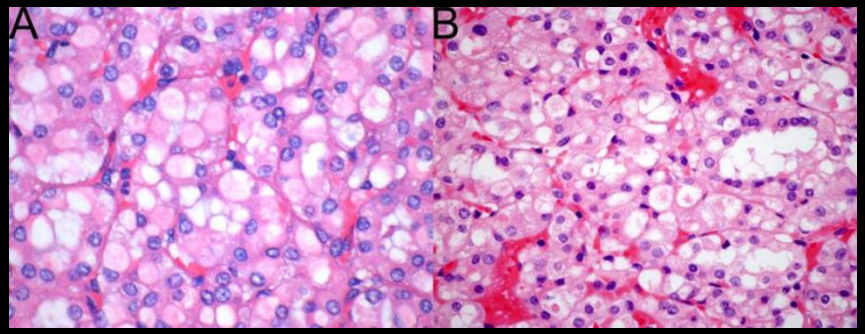
KIT, KIT proto-oncogene receptor tyrosine kinase; PDGFRA, Platelet-derived growth factor receptor A; DOG1, Discovered on GIST-1; IHC, Immunohistochemistry.
*To date, a single succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumour (GIST) arising in the duodenum has been reported.[43]

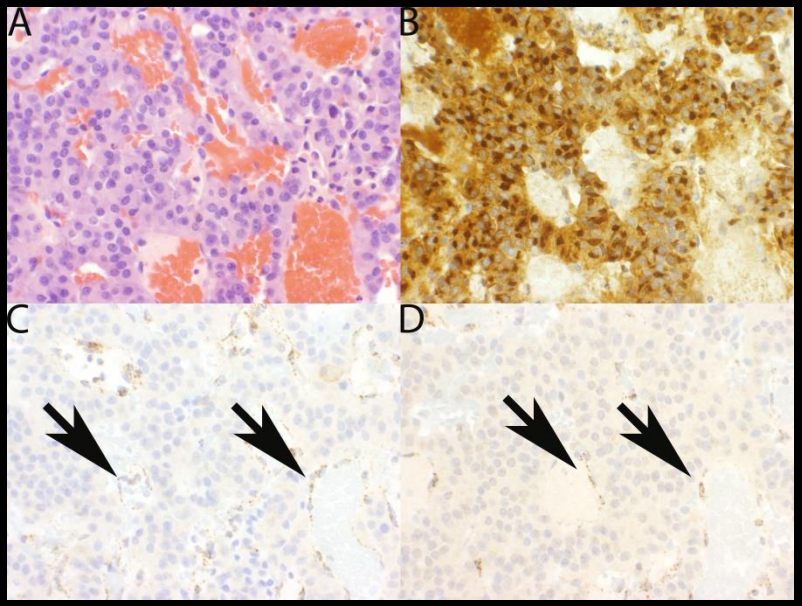
Gill AJ Succinate dehydrogenase (SDH) deficient neoplasia Histopathology 2018; 72:106–116

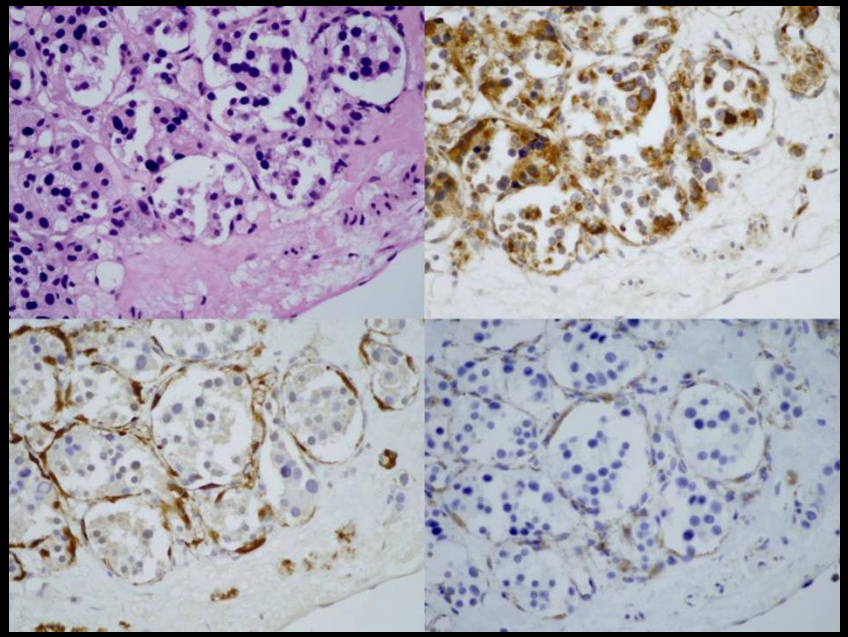
Diseases associated with SDH

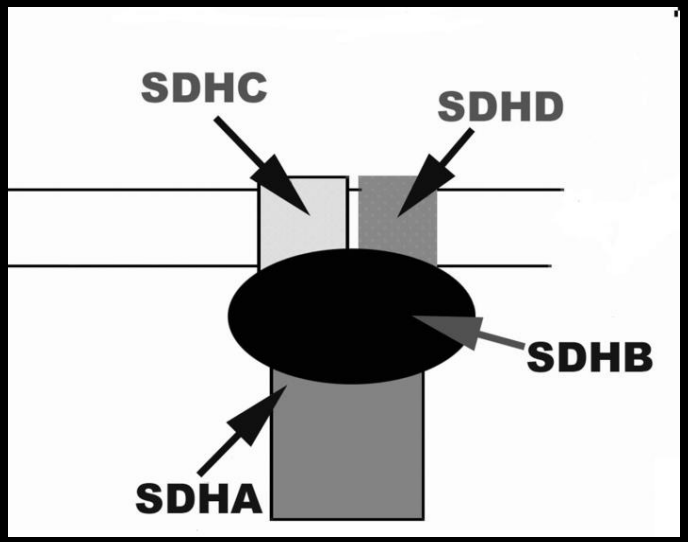
- Paragangliomas/Pheochromocytomas
- Pituitary adenomas
- A unique subtype of GISTs (“SDH deficient GISTs”)
- A unique type of renal carcinoma

SDH deficient GIST is only one part of a syndrome which includes pheochromocytoma/paraganglioma, renal carcinoma and pituitary adenoma









October 2018
Molecular pathology of GISTs

KIT mutation 80-85%

PDGFRA mutation 5-10%

SDH Deficient (3% = 5 to 7.5% of Gastric GISTs)

BRAFV600E mutant 1%

NF1 mutant 1%

KRAS/NRAS <1%

. . . getting close to 100% of GISTs with known mutations. . .

Now if there is a true wild type GISTs the diagnosis should be questioned

BRAFV600E mutant GISTs

1- 2.8% of GISTs have a BRAFV600E mutation

Usually exclusive with other mutations (1 case as acquired mutation)

Typical spindled cell morphology (look like KIT mutant GIST)

Arise in small intestine

Positive for KIT and DOG1 by IHC

Can be identified by mutation specific IHC for BRAFV600E

May respond to targeted therapy with BRAF inhibitors (vemurafenib or dabrafenib)

BEFORE MAKING THE DIAGNOSIS OF BRAFV600E MUTANT GIST PLEASE CONSIDER THE POSSIBILITY OF METASTATIC MELANOMA

Ref: Agaram NP, Wong GC, Guo T et al; Genes Chromosome and Cancer 2008;47:853-859
Hostein I, Faur N, Primois C et al; Am J Clin Pathol 2010; 133:141-148

Neurofibromatosis associated GISTs

1% of all GISTs

Arise in 7% of patients with neurofibromatosis 1

Show somatic mutation or loss of wild-type allele

Frequently multifocal

Typical spindle cell morphology

Small bowel location

Less aggressive

Lack KIT or PDGFRA mutations

Consider NF1 in a Wild type GISTs

Predictive molecular pathology for GIST

KIT and PDGFRA mutation in 85-90% of GISTs

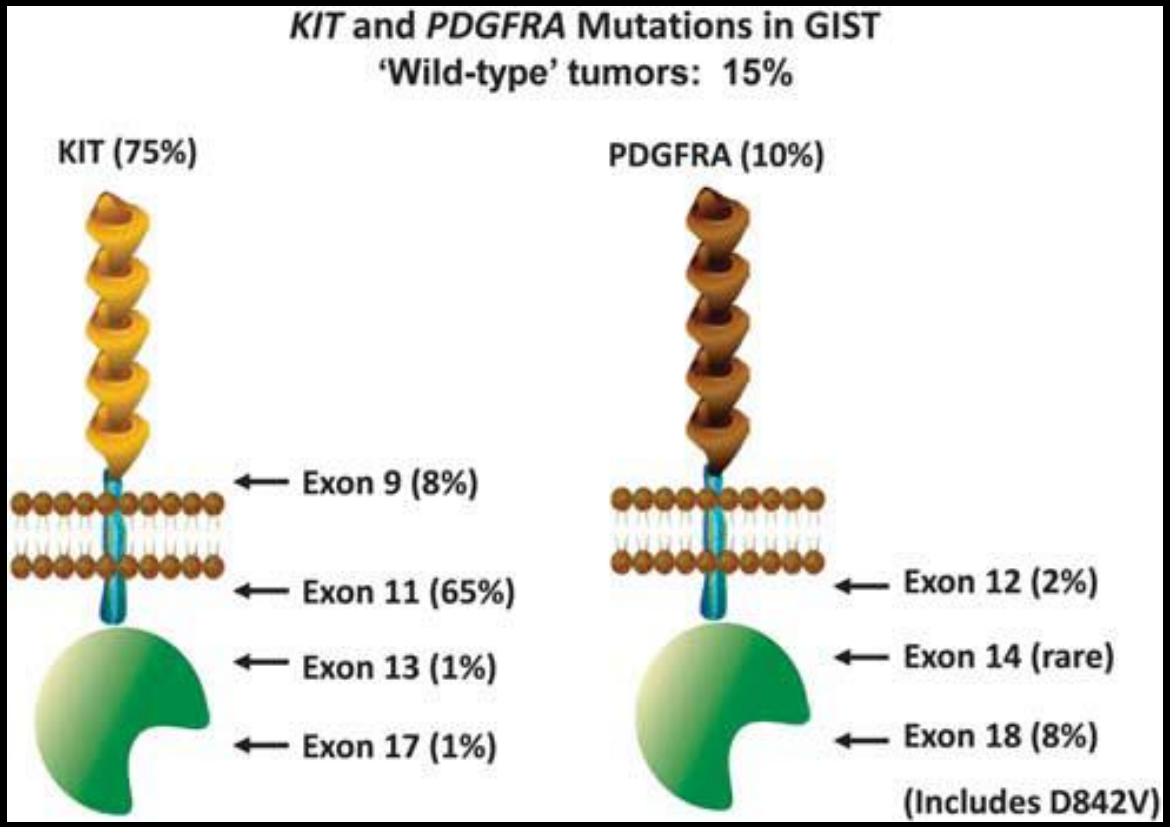
KIT and PDGFRA are highly synonymous, both on chromosome 4q.

Created by a gene duplication event. PDGFRA has one more exon.

Both are TYPE III RTKs (receptor tyrosine kinases).

EC

JM
TK1
TK2



Corless CL Gastrointestinal Stromal Tumours: what do we know now? Modern Pathology 2014 27:S1-S16

KIT and PDGFRA mutation in 85-90% of GISTs

KIT and PDGFRA mutations are mutually exclusive

KIT mutations

– 80 to 85% of all GISTs

Exon 9 – 9%

Exon 11 – 67%

Exon 13 – 1%

Exon 17 – 1%

PDGFRA mutations

– 5 to 10 % of all GISTs

Exon 12 (2%)

Exon 14 (rare)

Exon 18 (5.5%)

PDGFRA mutant GISTs

5-10% of all GISTs

Mostly gastric (and E-GIT) location

Epithelioid

Giant cells

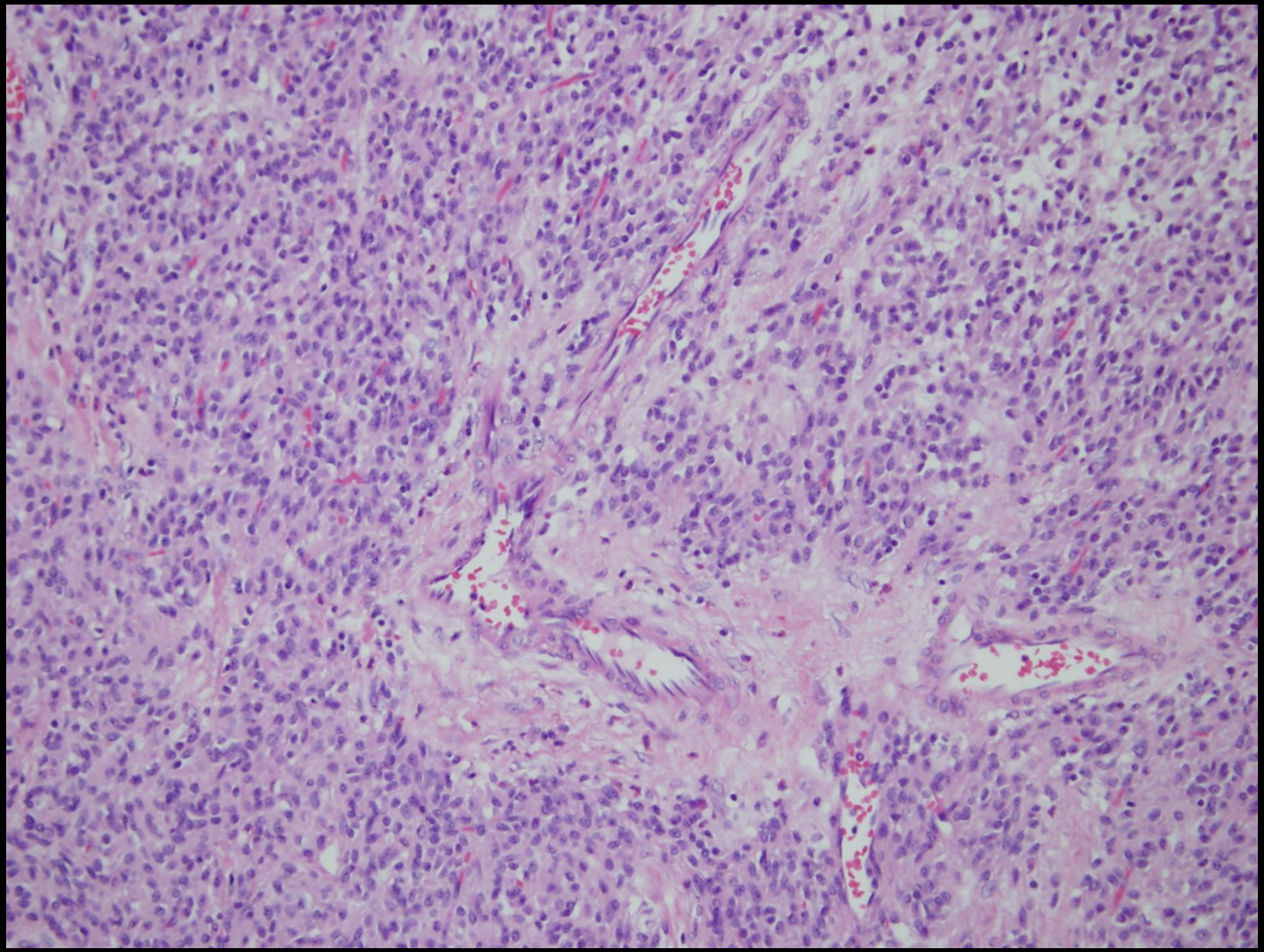
Myxoid stroma

Multinucleate cells

Rhabdoid morphology

Commonly KIT IHC neg/focal but DOG1 pos

Better prognosis than KIT negative GISTs



PDGFRA mutant GIST – Gastric location, epithelioid morphology, often with scattered multinucleate or bizarre cells, DOG1 positive, CKIT negative or focal

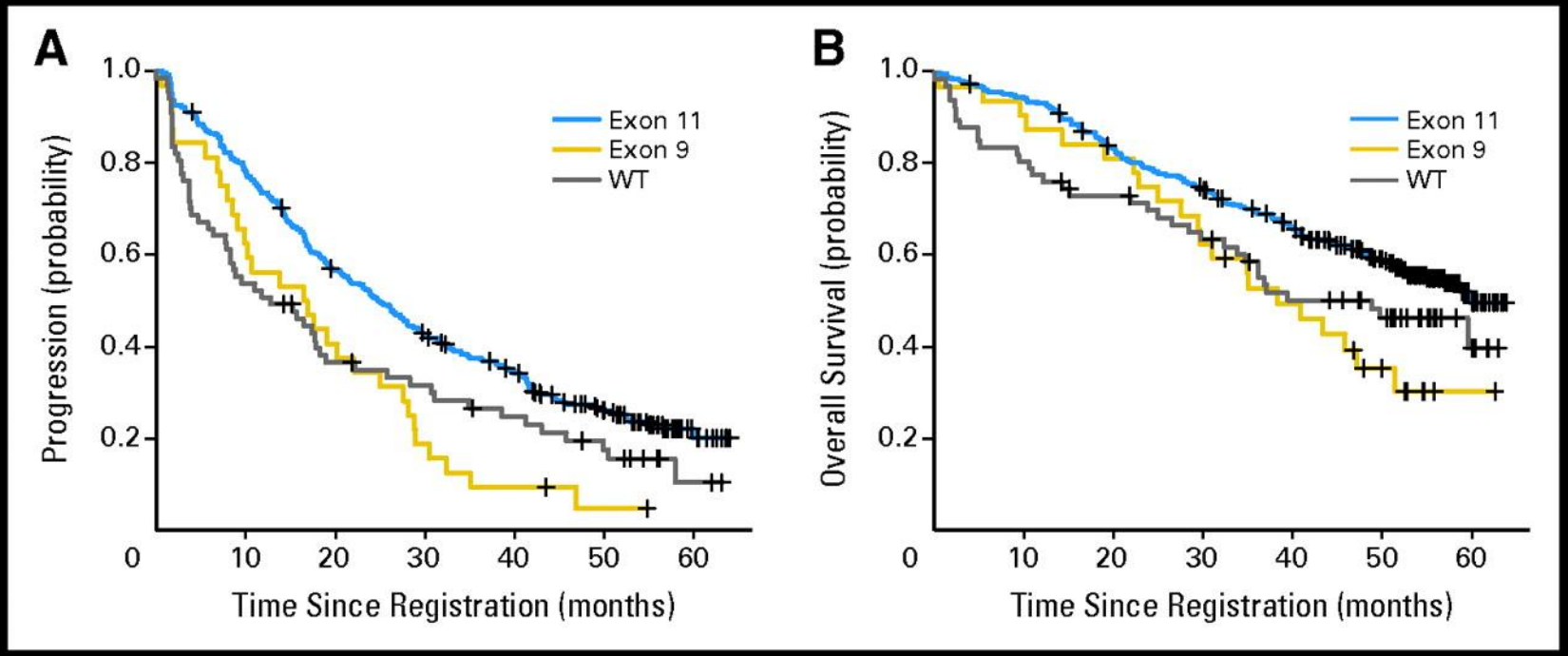
Primary Imatinib Resistance (10-30%)

Defined as tumours which progress in 3-6mths of starting therapy

- KIT and PDGFRA wild type GISTs
- KIT exon 9 mutants
- Most common PDGFRA mutant GIST (exon 18 - D842V) – 5% - refractory to all treatment.

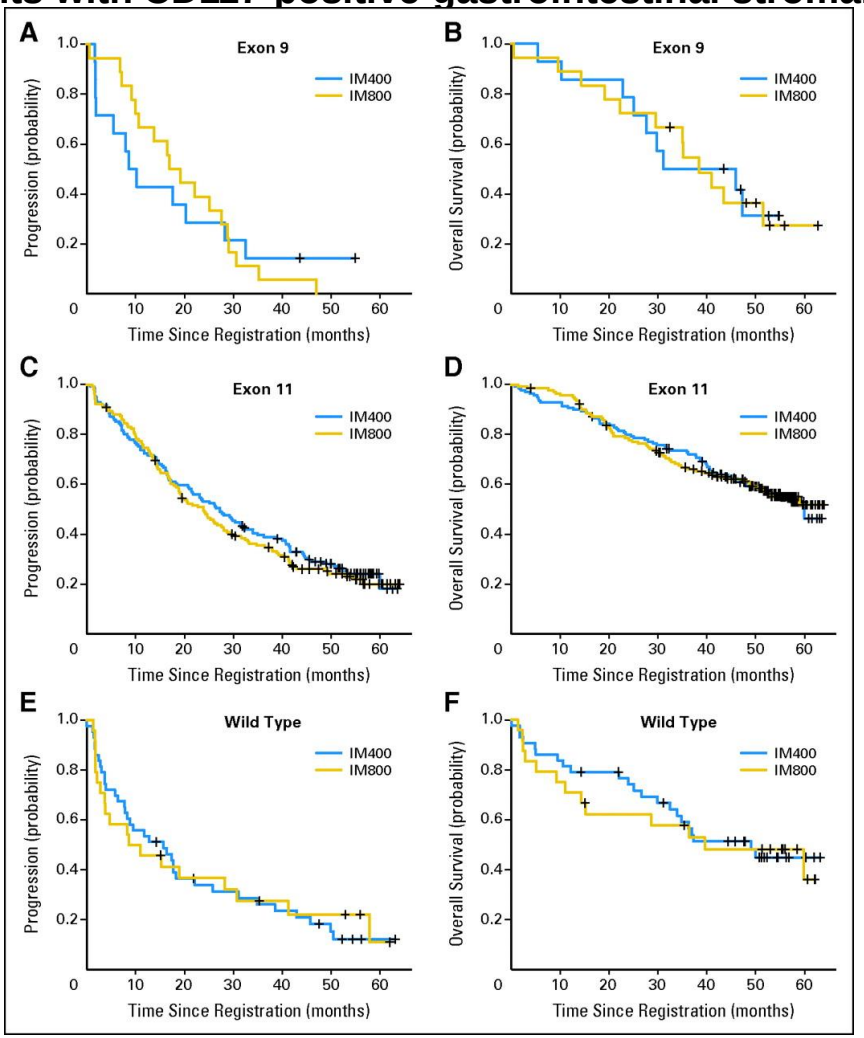
PDGFRA exon 19 – D842V – Devil's mutation

KIT mutant GISTs (80-85%)



Michael C. Heinrich et al. JCO 2008;26:5360-5367

Correlation of tumor genotype (KIT exon 9–mutant, KIT exon 11–mutant, or wild-type tumors), imatinib dose (400 mg [IM400] v 800 mg [IM800]), and time to progression and overall survival for patients with CD117-positive gastrointestinal stromal tumors.



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Delayed/Secondary Resistance (50%)

- Defined as resistance after 6mths
- Usually occurs in first 2 years (50%)
- Resistance can be limited to one nodule or be generalized
- Usually different nodules usually have different resistance through acquired secondary mutations – classic clonal selection

Delayed/Secondary Resistance (50%)

- Secondary mutations are found in >80% of drug resistant-GISTs
- Most common mechanisms is intra-allelic second mutations that encode the ATP binding site or activating loop
- Sunitinib – good activity against exon 13 to 14 resistance mutations
- Regorafenib (+sorafenib) good activity against exon17 to 18 resitance mutations

Molecular assessment GIST

Most authorities recommend mutation testing whenever therapy is being commenced or when secondary resistance occurs

- cKIT exons 9, 11, 13, 17
- PDGFRa exons 18,12,14

KIT/PDGFRA mutation status is associated with outcome, but size/mitotic rate is the most important determinant

Favourable mutations:

PDGFRA mutation

KIT exon 11 duplication mutations

Deletion of a single codon of exon 11 (leading to Trp557Arg, Val559Ala, orLeu576Pro have a low risk of recurrence)

ALL HAVE A FAVOURABLE OUTCOME

The standard size/mitotic rate algorithm over-estimated the risk for these favourable mutants

Patients with unfavourable mutations (eg: KIT exon 9 mutation leading to Ala502_Tyr503 duplication or deletions that involve amino acids 557 and 558 of exon 11), were still at low risk for GIST recurrence, provided that the mitotic count was very low

Patients with PDGFRA mutation have a high risk of recurrence if high mitotic rate

Joensuu H, Rutkowski P, Nishida T et al KIT and PDGFRA Mutations and the Risk of GI Stromal Tumor Recurrence Journal of Clinical Oncology 2015;33:634-642

Molecular subgroup	Prognostic relevance after R0	Adjuvant treatment	Palliative treatment
KIT exon 11 duplication mutation of one codon or deletion of one codon only	Genotype associated with excellent prognosis	None for intermediate risk GIST	Imatinib 400 mg
KIT exon 11 mutations upstream of codon 557			Longer median PFS (49 months)
KIT exon 11 deletions involving codon 557 and 558	Higher risk of recurrence	Consider adjuvant treatment for intermediate risk GIST	Imatinib 400 mg; shortest median PFS of KIT exon 11 mutations (31 months)
KIT exon 11 mutations downstream of codon 558			Longest median PFS (63 months)
KIT exon 11 mutation other than above	Genotype not independent predictor	General recommendations	Imatinib 400 mg; nilotinib 800 mg as second line might be considered (only in case of intolerance to imatinib)
KIT exon 9	Genotype not independent predictor	Imatinib 800 mg can be considered for adjuvant treatment (not backed by clinical trial)	800 mg imatinib with improved PFS and RR; patients starting with 400 mg benefit from dose-escalation; refractory to nilotinib (do not use in case of imatinib-intolerance)
PDGFRA D842V; PDGFRA DI842-843IM	Probably independent favorable prognostic factor	None	Clinical trial: BLU-285; crenolanib
PDGFRA mutations other than D842V/DI842-843IM	Probably independent favorable prognostic factor	General recommendations in patients considered at high risk	Imatinib 400 mg
Nonsyndromic wild type GIST		Minimal prospective data	Consider genotyping for BRAF, NRAS, NF1; consider clinical trial with inhibitors of PI3K or MAPK if positive
Syndromic GIST (NF-1, Carney, Carney–Stratakis)		Adjuvant treatment not recommended (limited prospective data)	Observe spontaneous growth; consider clinical trials

GIST, gastrointestinal stromal tumor; KIT, stem cell growth factor receptor; MAPK, mitogen-activated protein kinase; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; RR, response rate.

Pogorzelski M, Falkenhorst J, Bauer S Molecular subtypes of gastrointestinal stromal tumor requiring specific treatments Curr Opin Oncol 2016;28:331-337

October 2018
Molecular pathology of GISTs

KIT mutation 80-85%

PDGFRA mutation 5-10%

SDH Deficient (3% = 5 to 7.5% of Gastric GISTs)

BRAFV600E mutant 1%

NF1 mutant 1%

KRAS/NRAS <1%

. . . getting close to 100% of GISTs with known mutations. . .

Now if there is a true wild type GISTs the diagnosis should be questioned

Quadruple Wild type GISTs

Quadruple wild type GISTs

Lack KIT, PDGFR, SDH, BRAF/RAS/NF1 mutations

Before diagnosis a wild type GIST . . . . . .
. . . . .

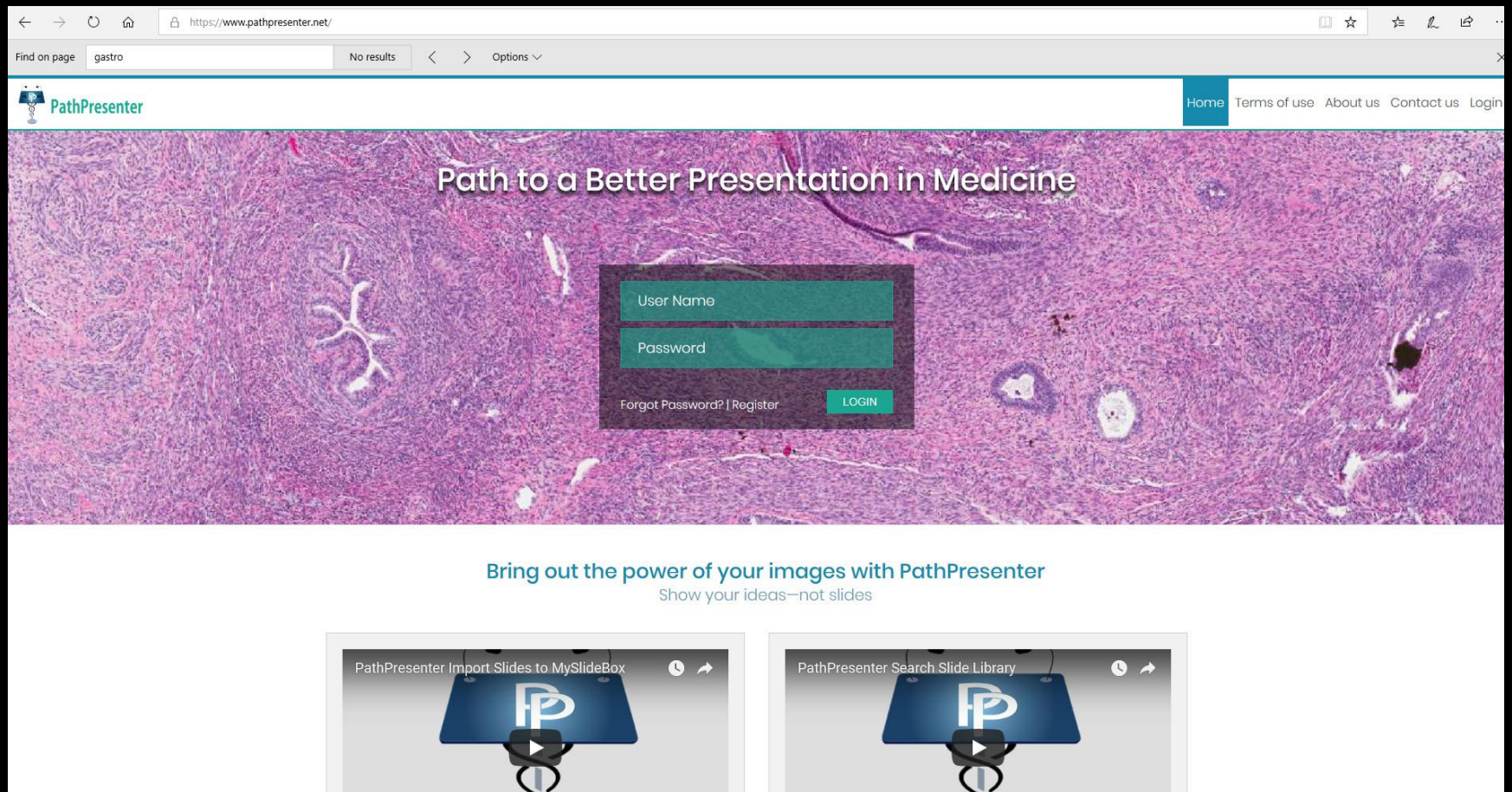
. . . . stop and ask could it be something else

Mesenchymal Tumours which are not GISTs

- Schwannoma
- Leiomyoma/Leiomyosarcoma
- Desmoid fibromatosis
- Inflammatory fibroid polyp
- Inflammatory myofibroblastic tumour
- Plexiform Fibromyxoma
- Glomus tumour
- Melanoma

PathPresenter

www.pathpresenter.net



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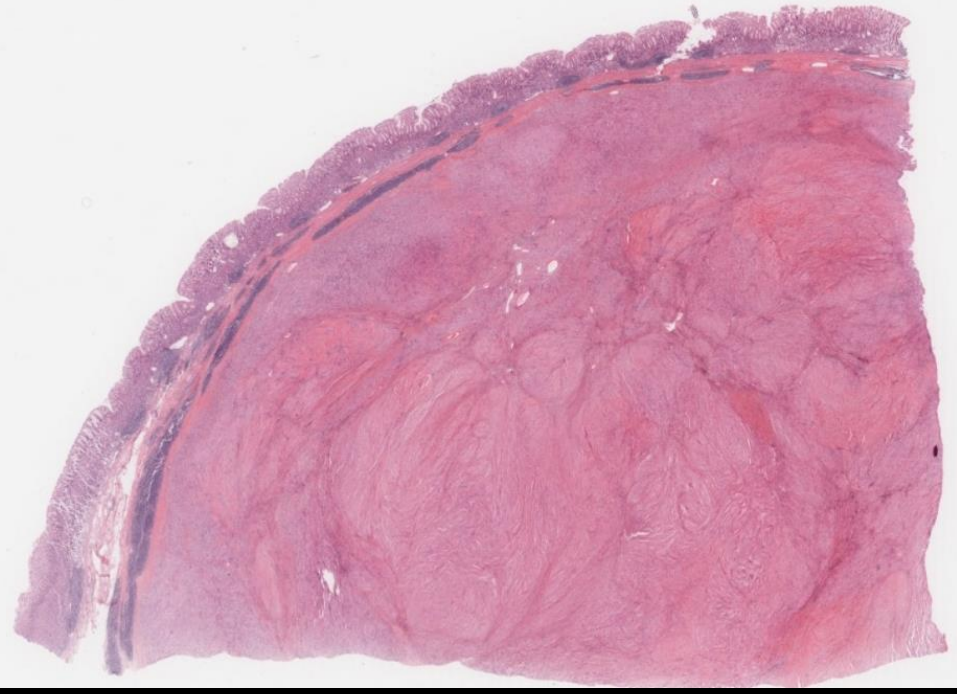

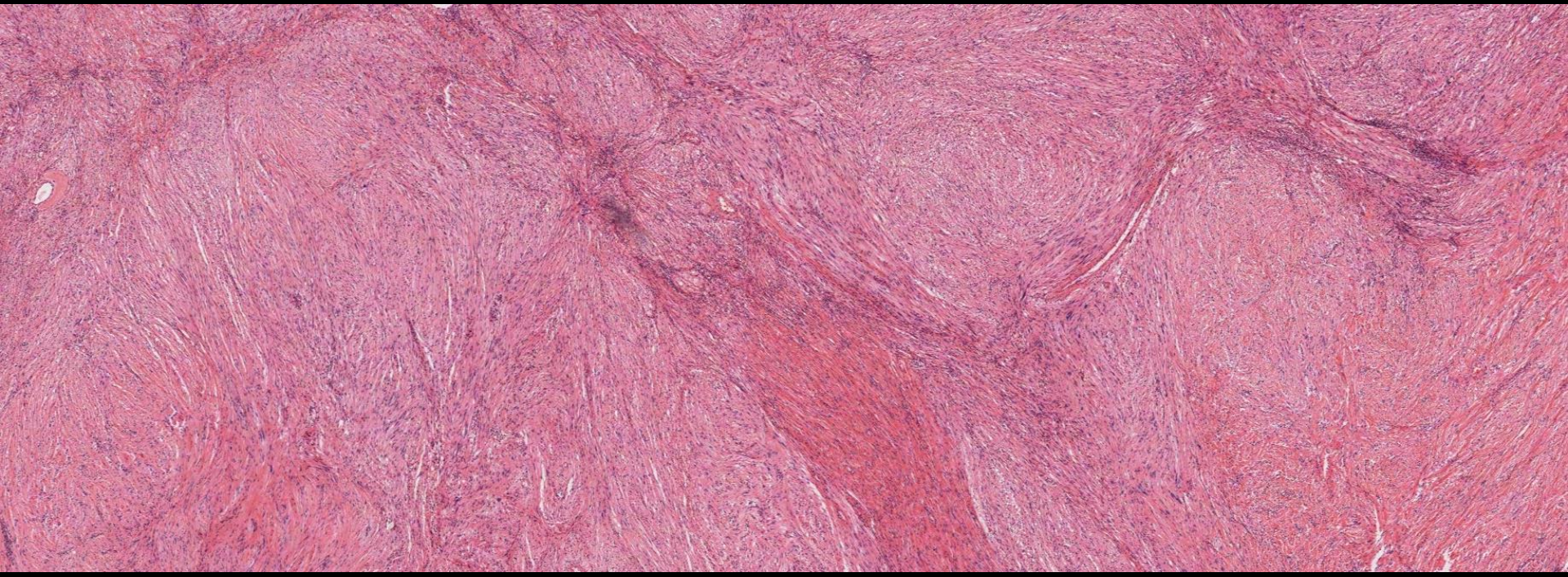

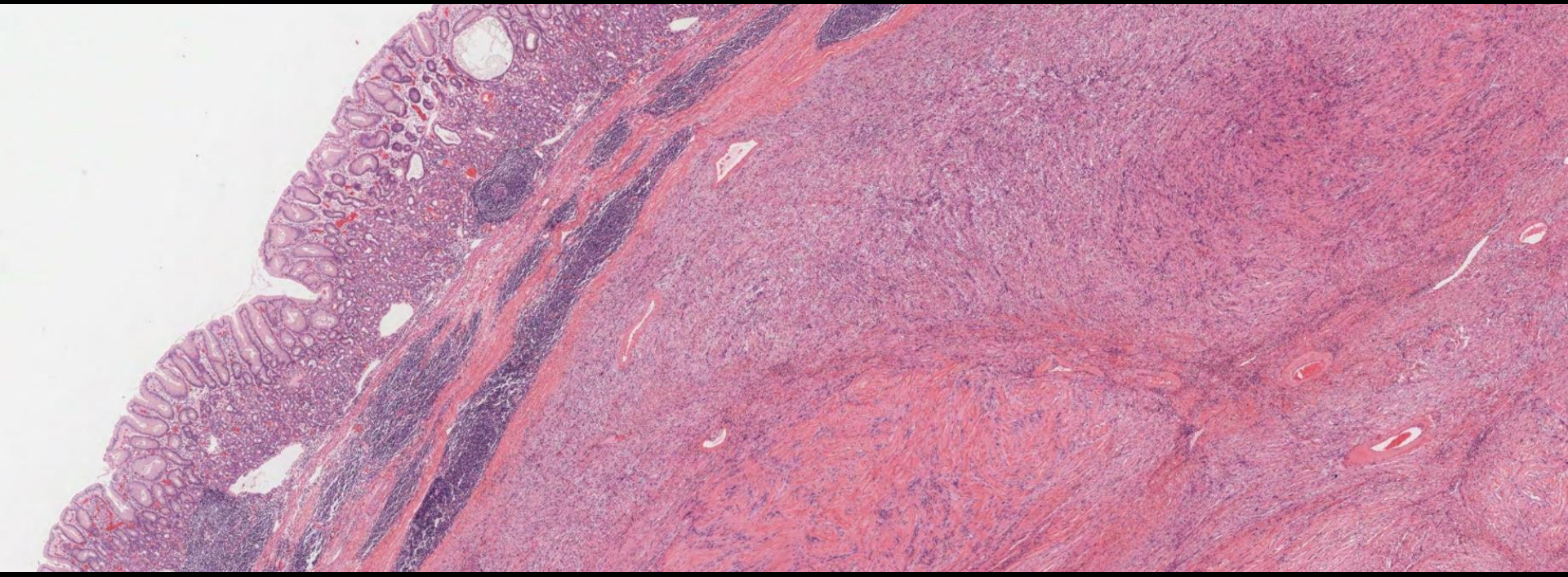

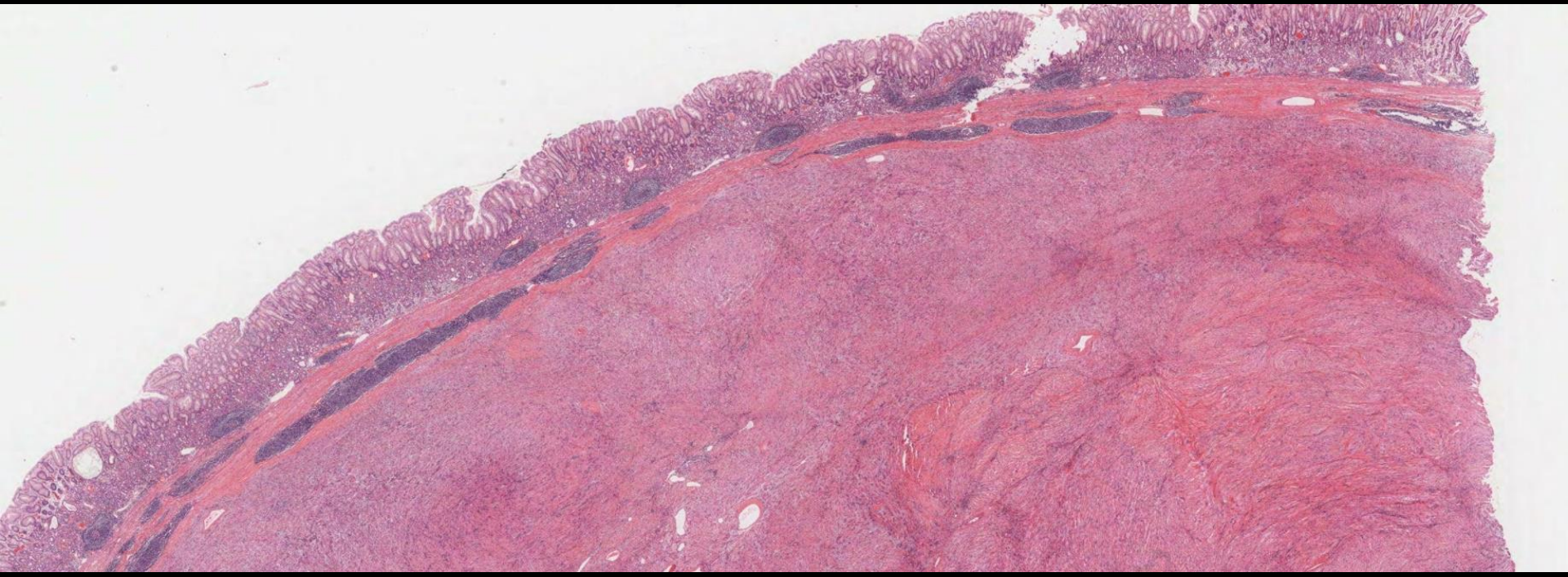

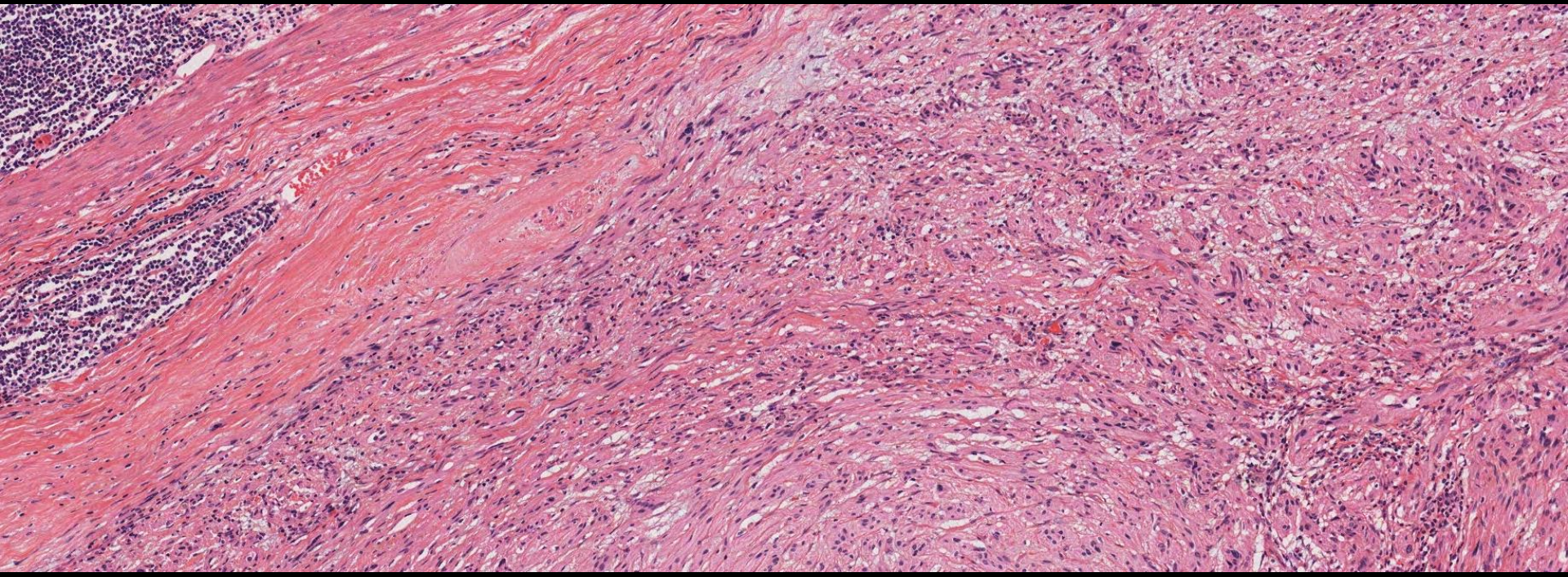

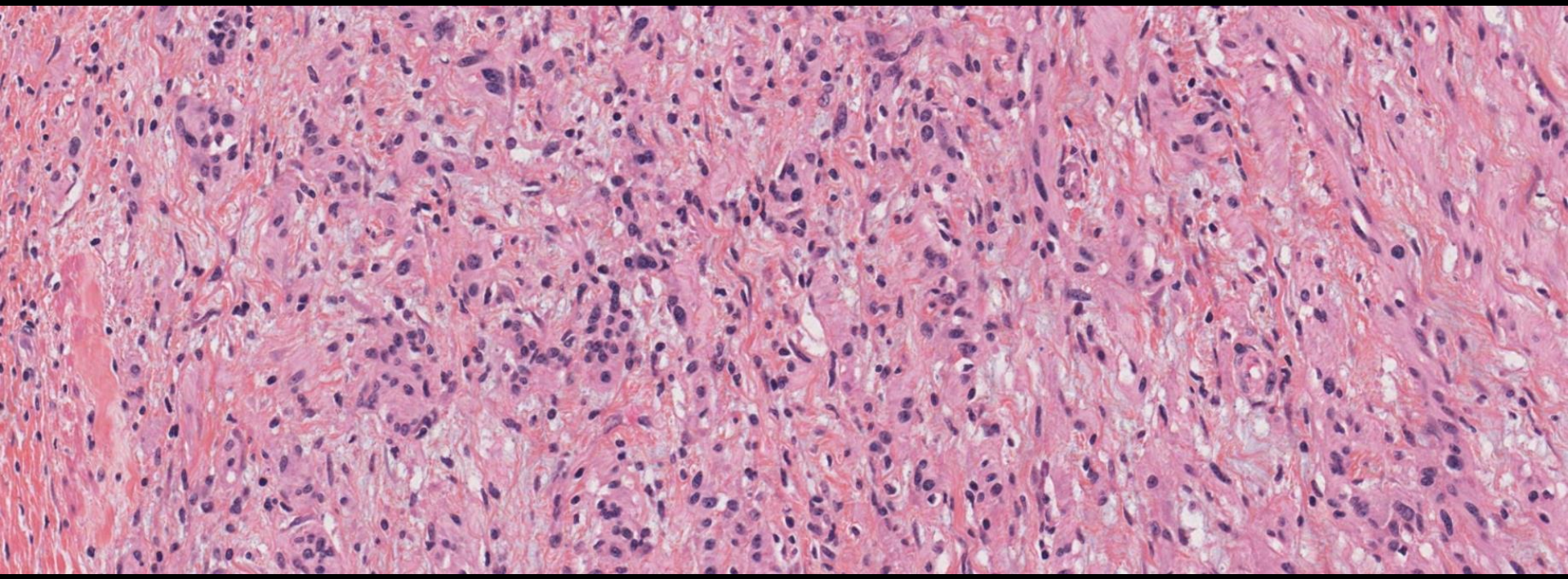

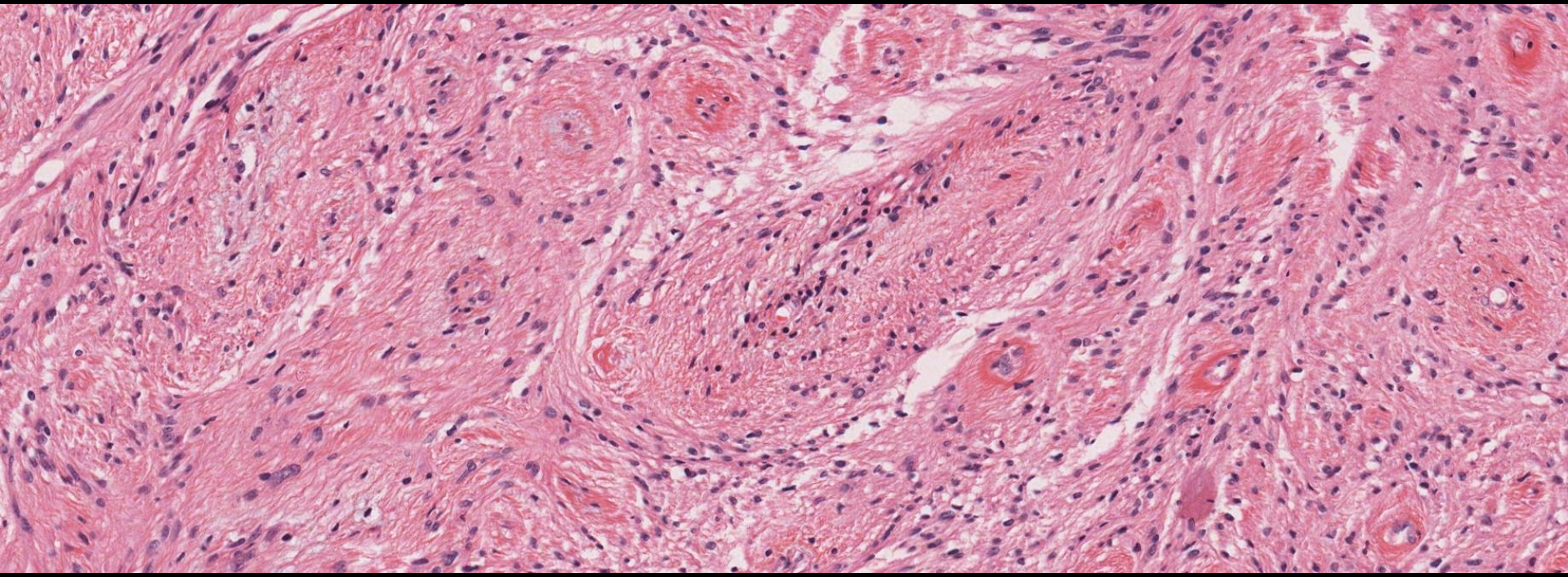

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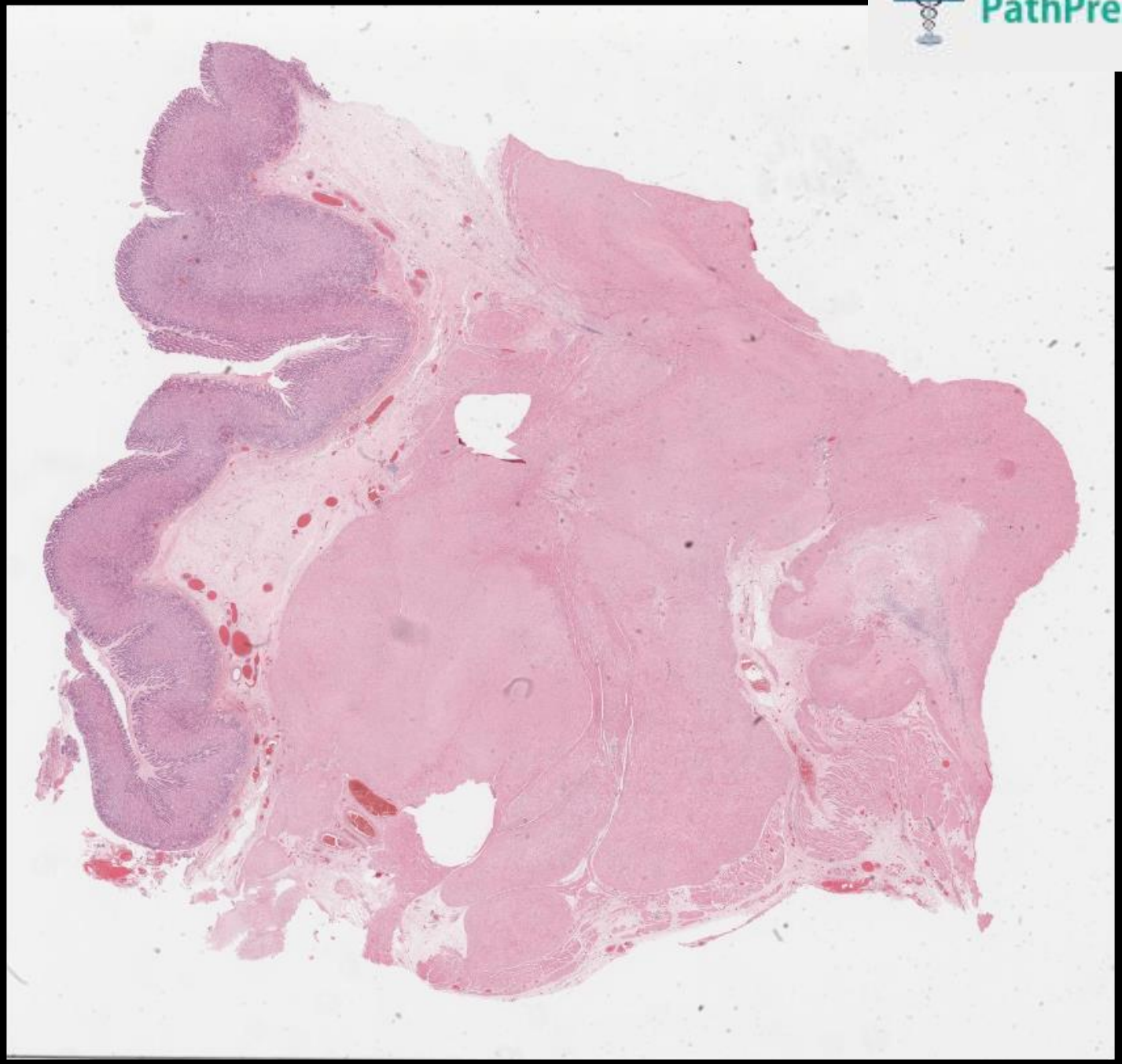

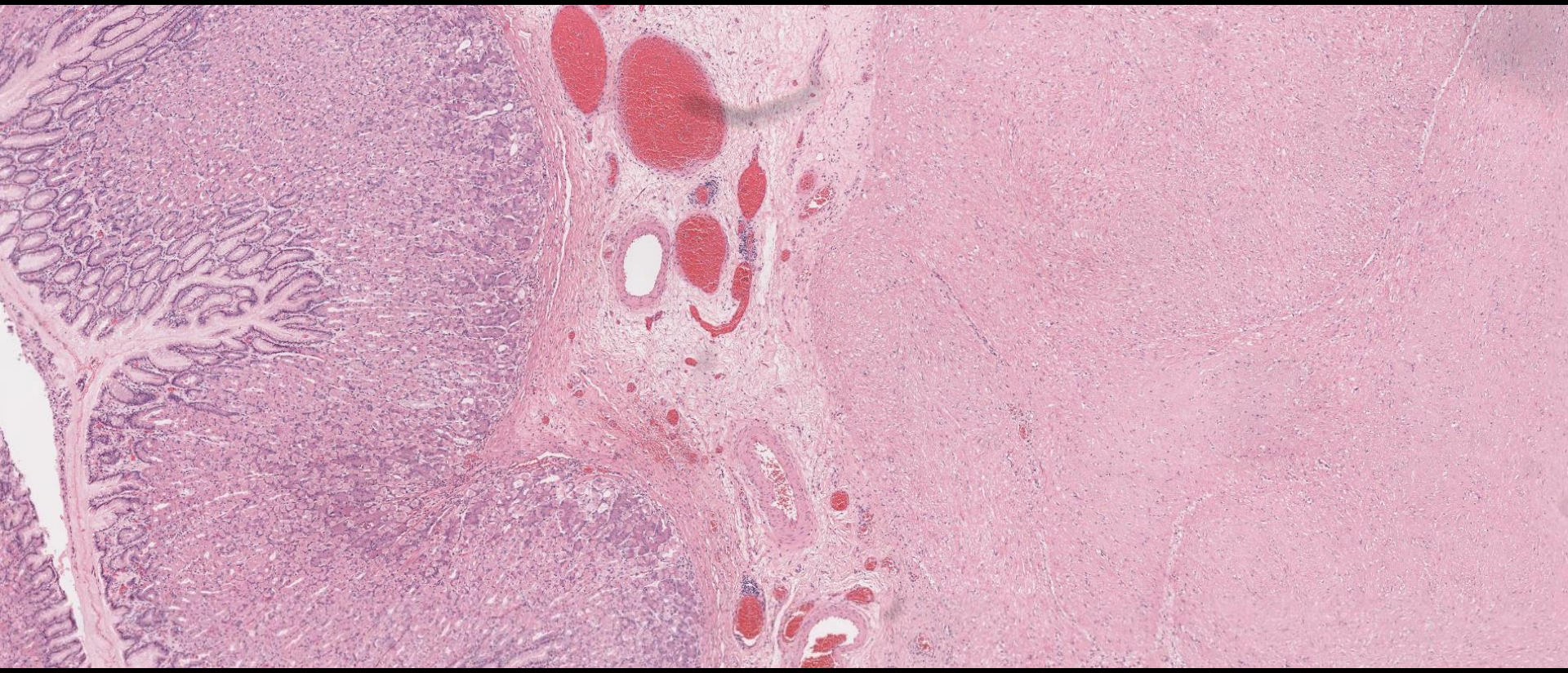

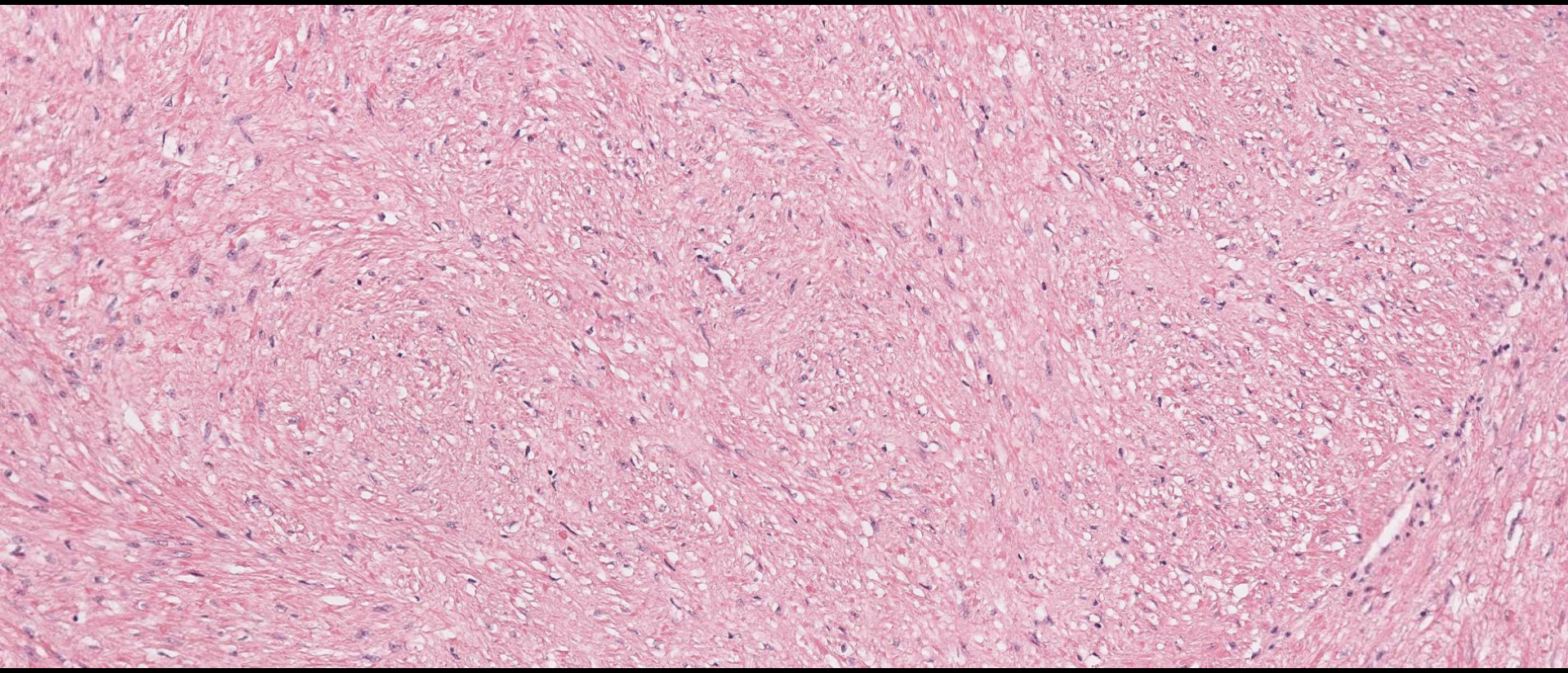

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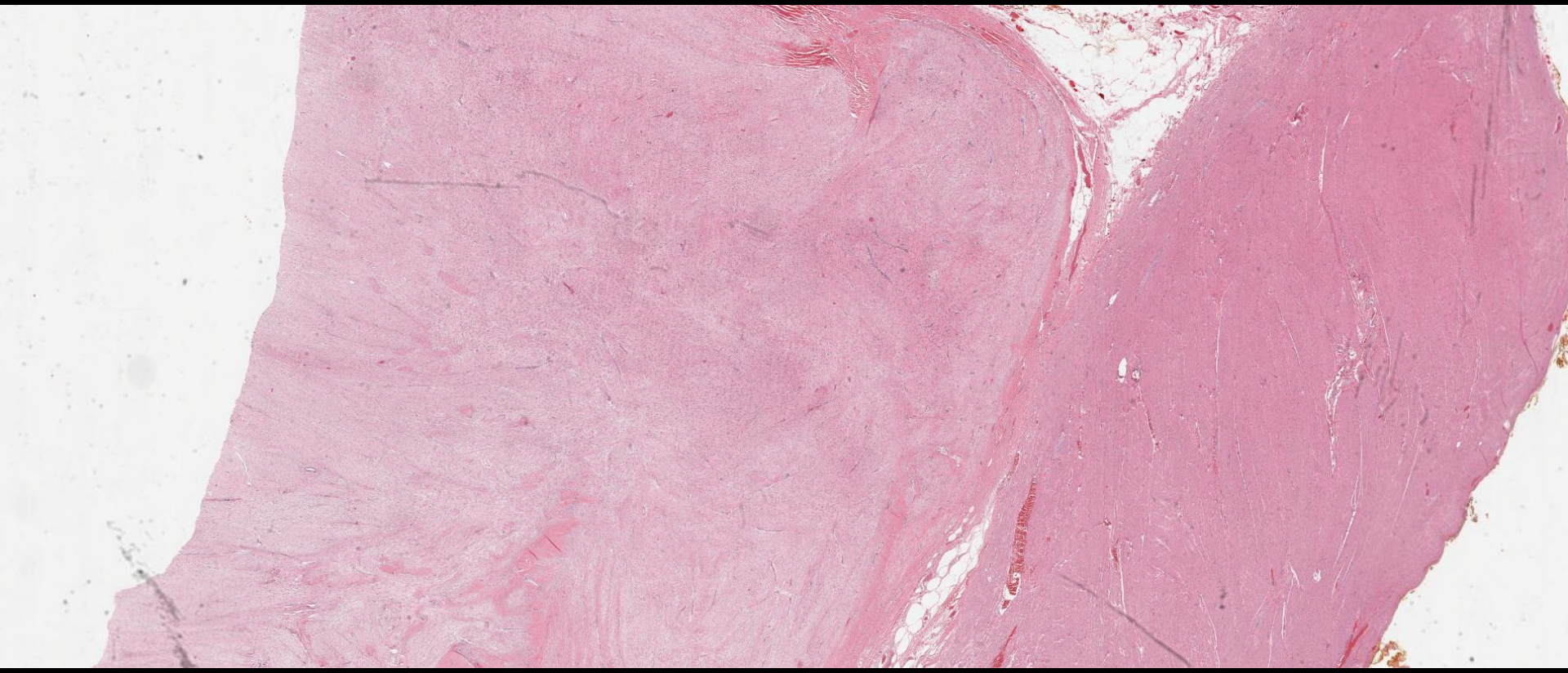

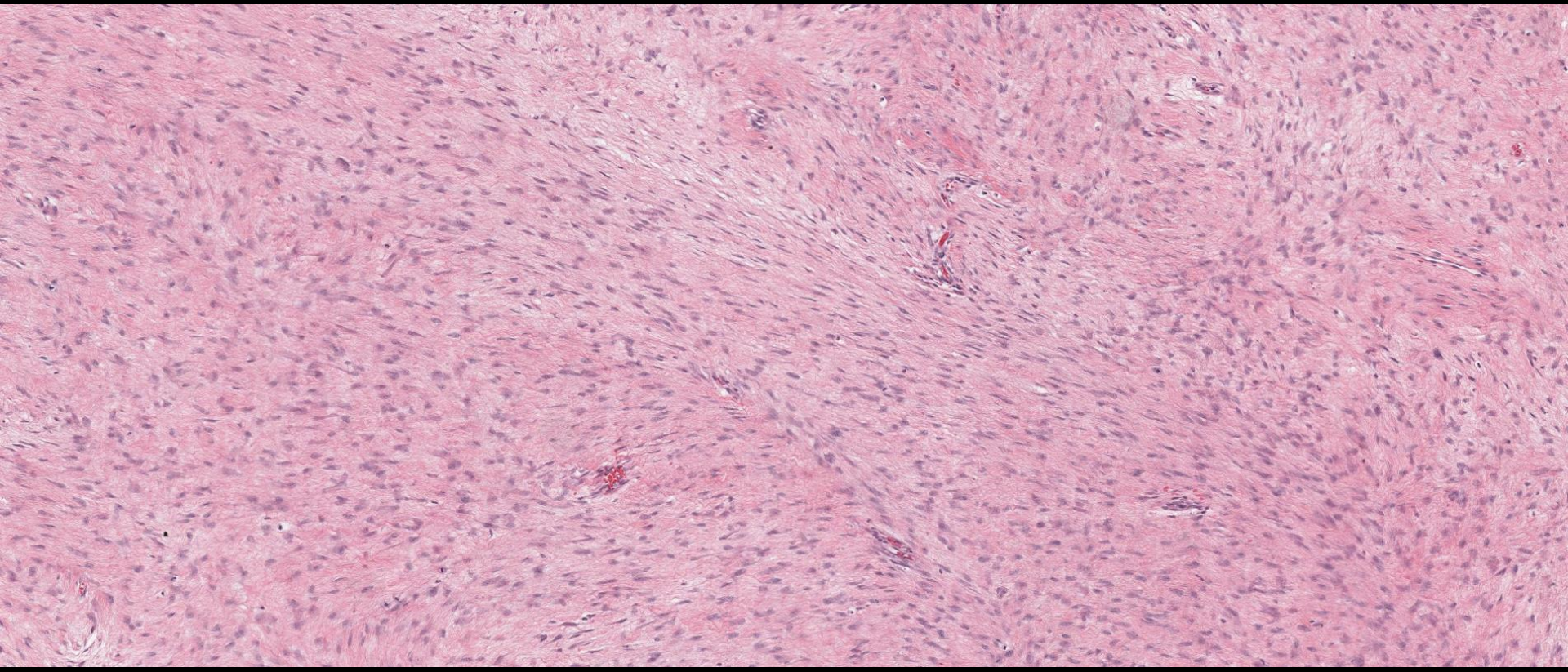

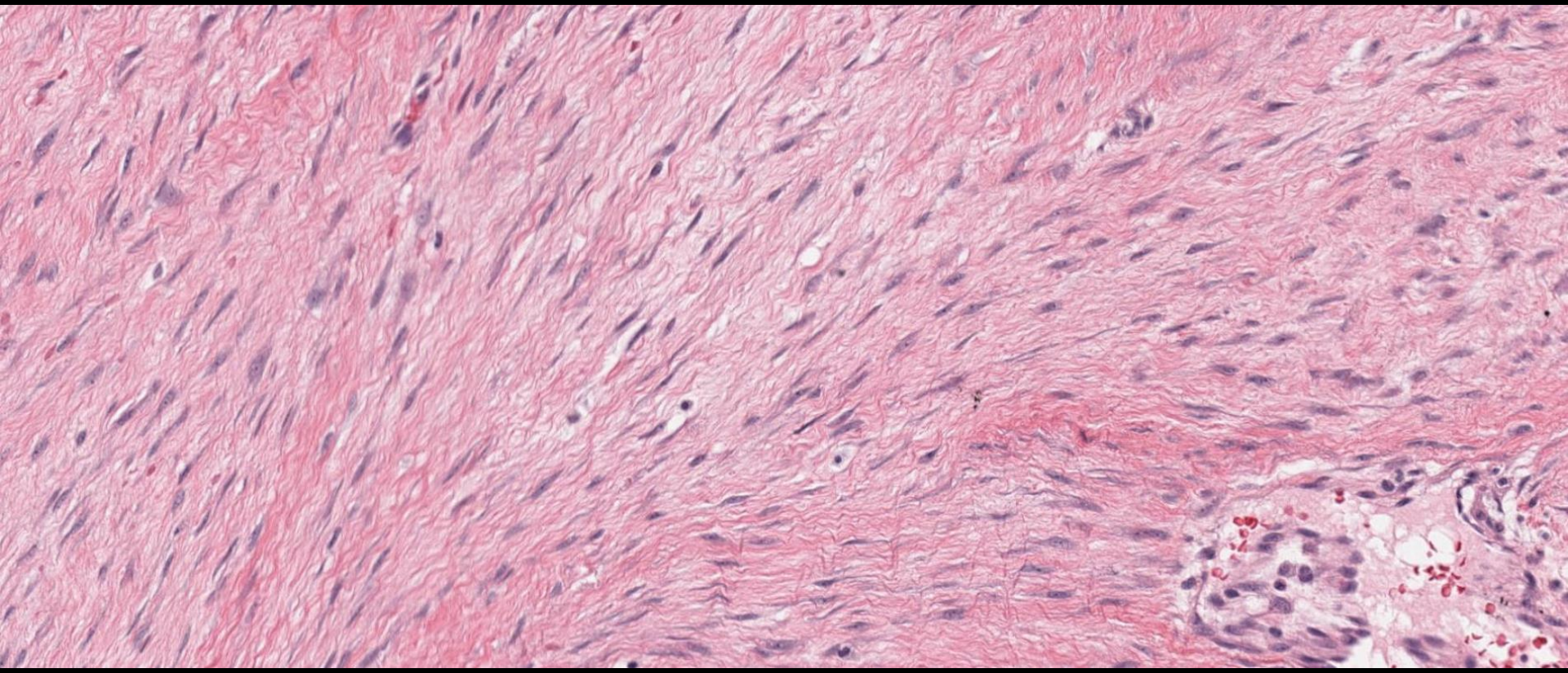

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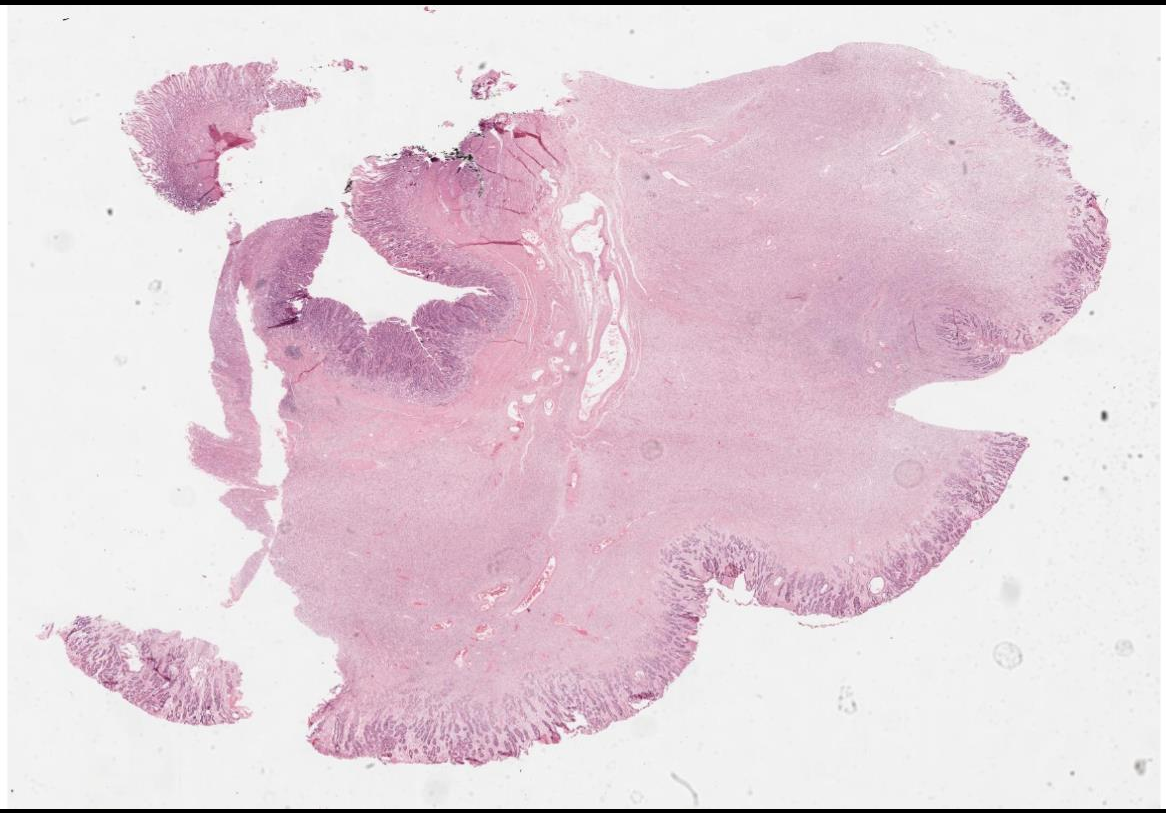

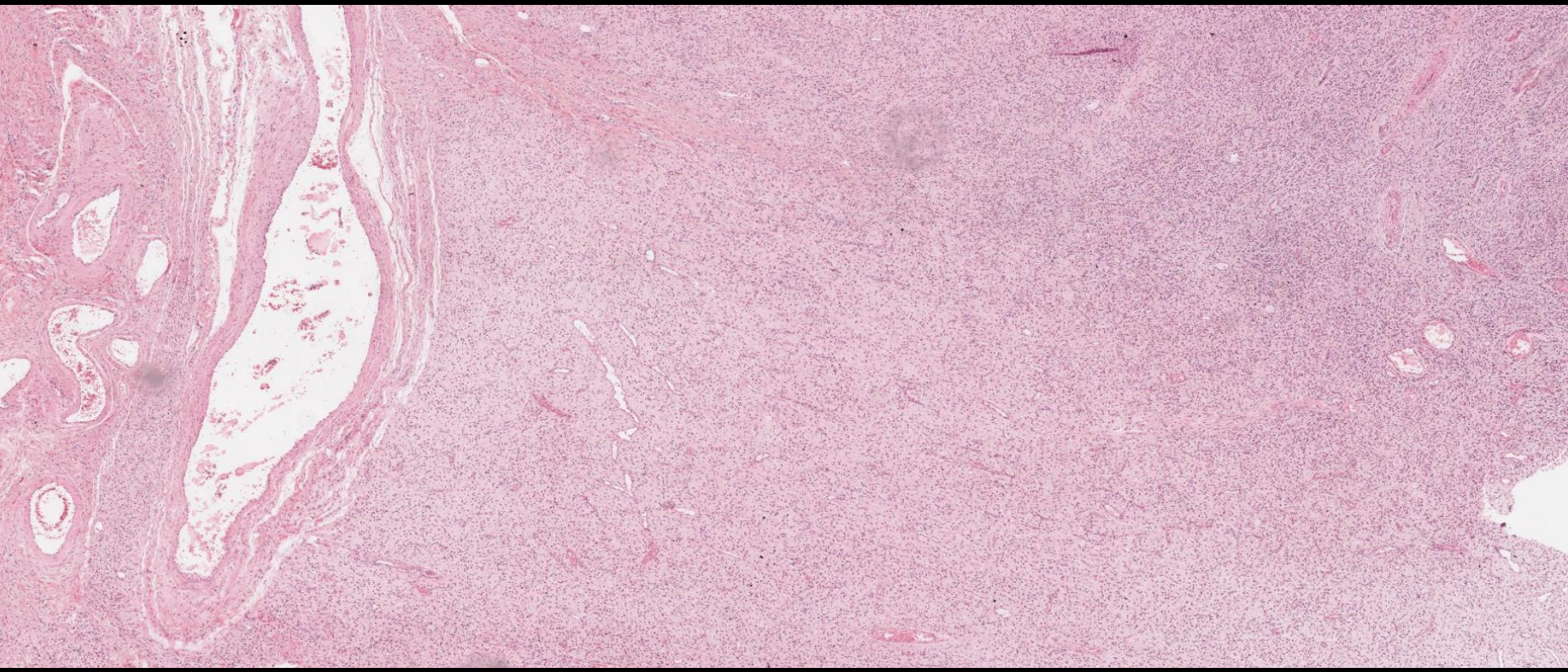

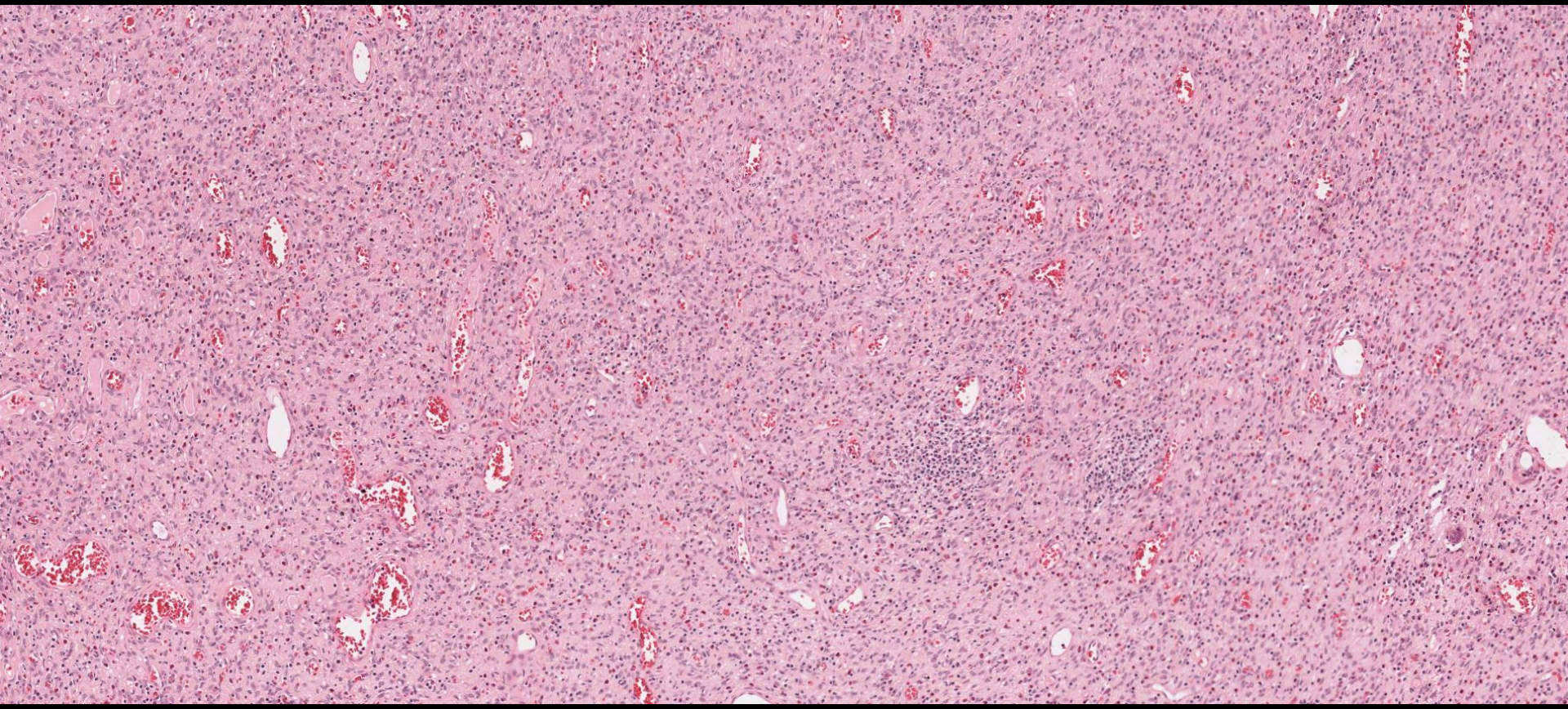

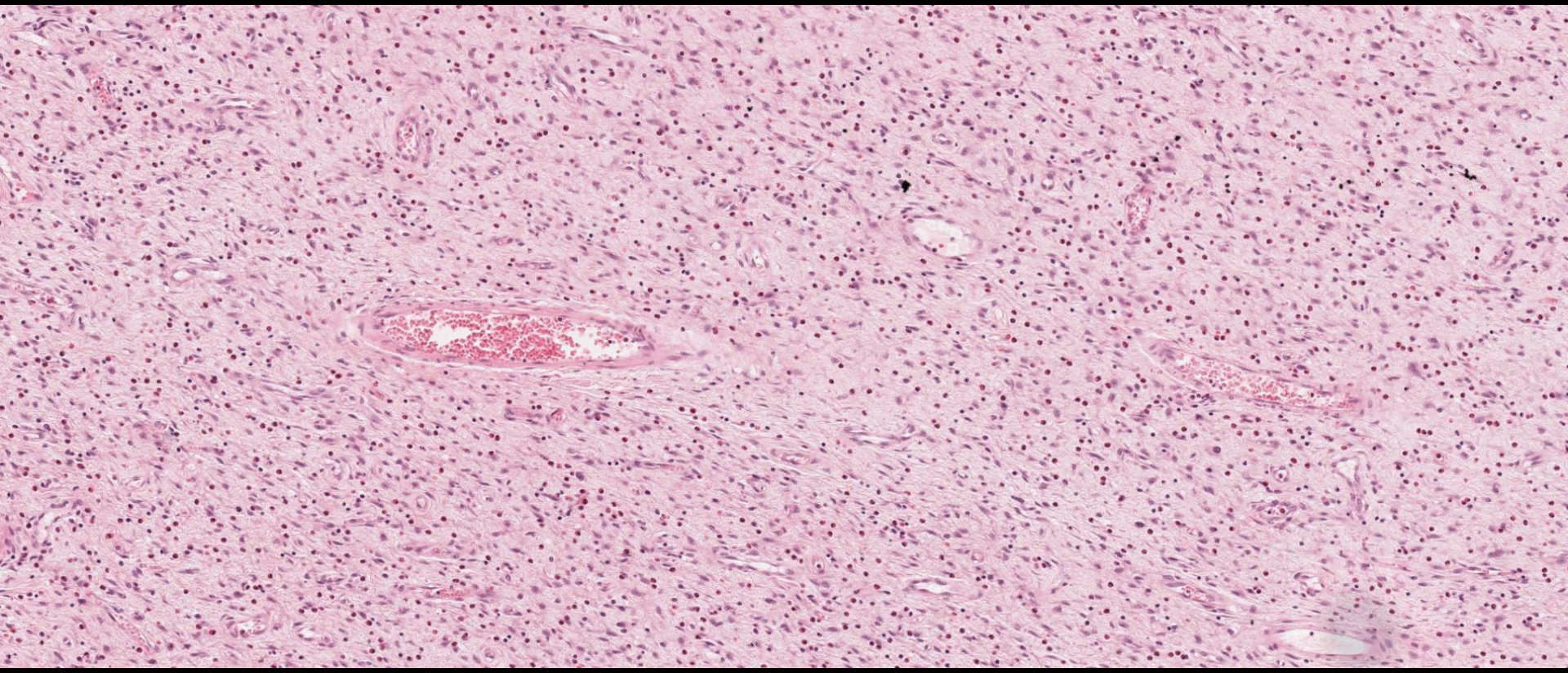

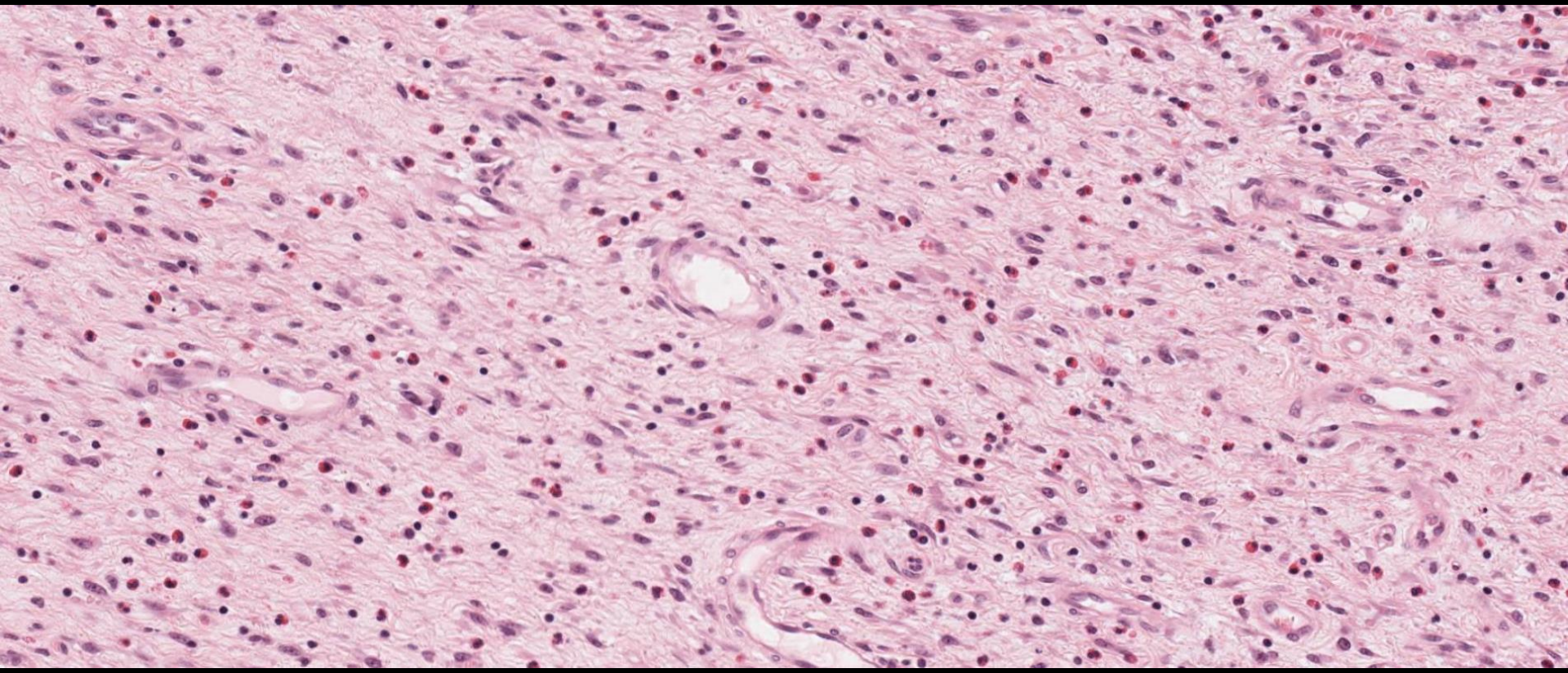

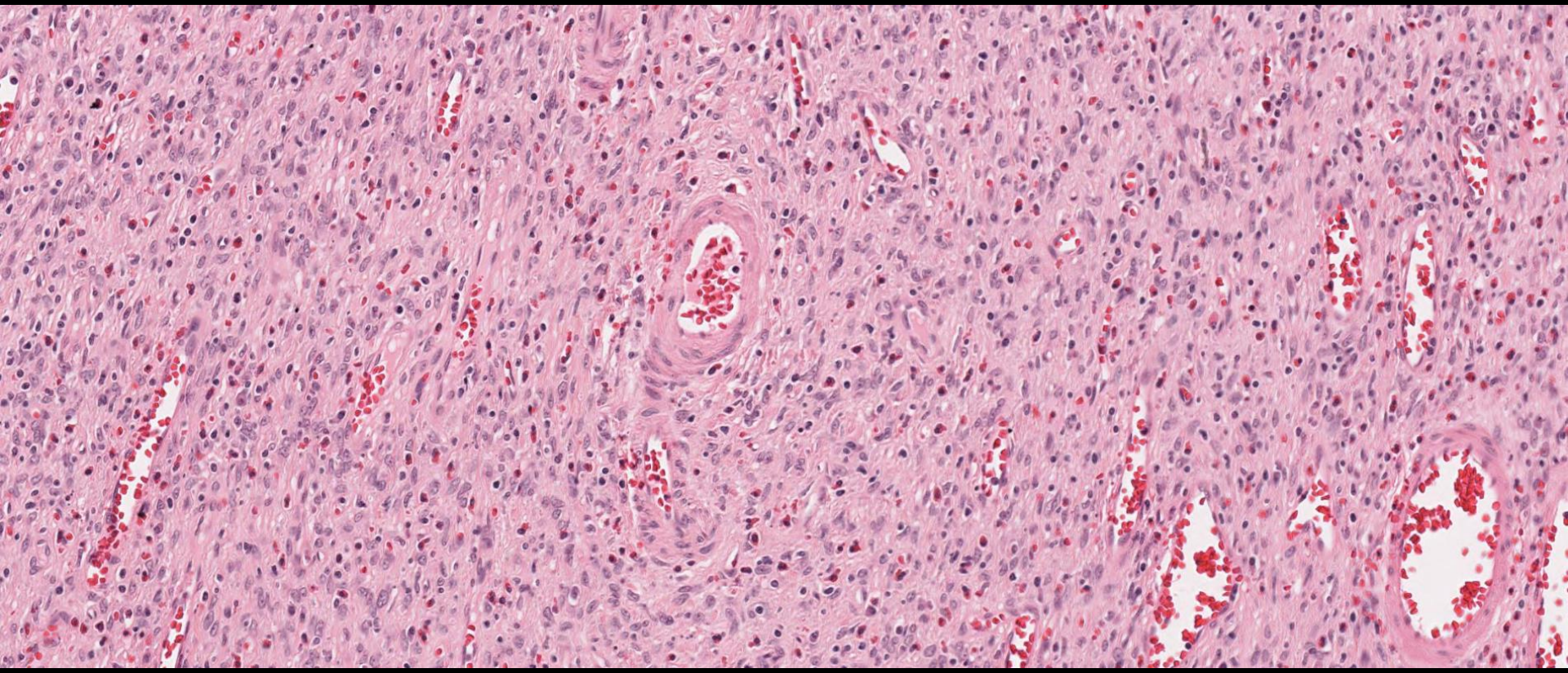

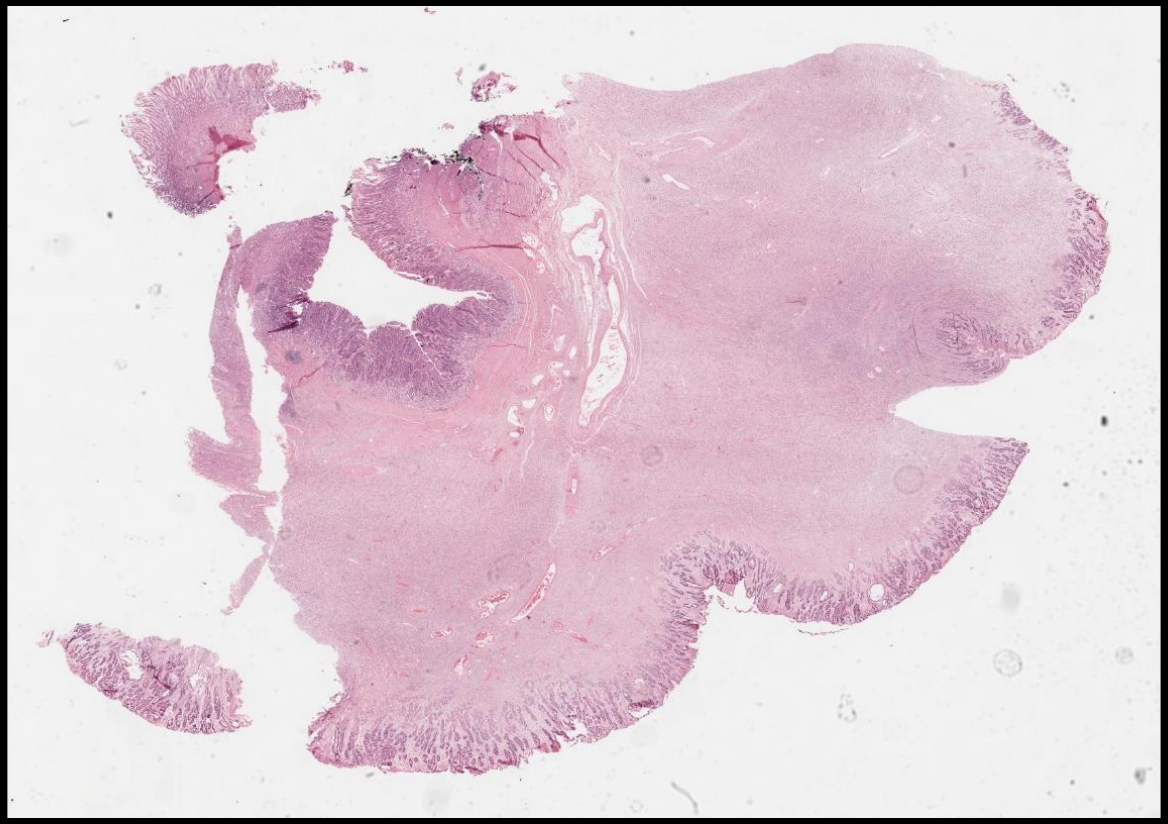

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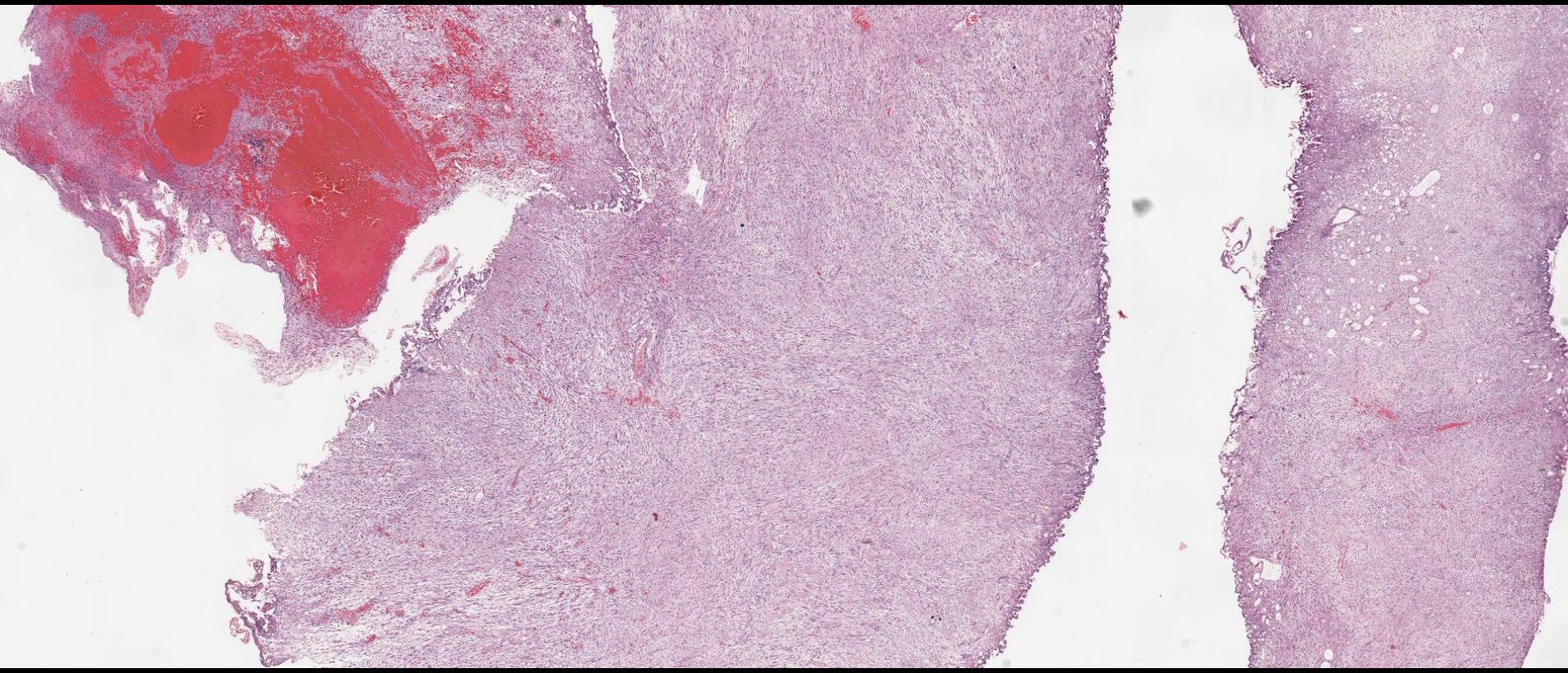

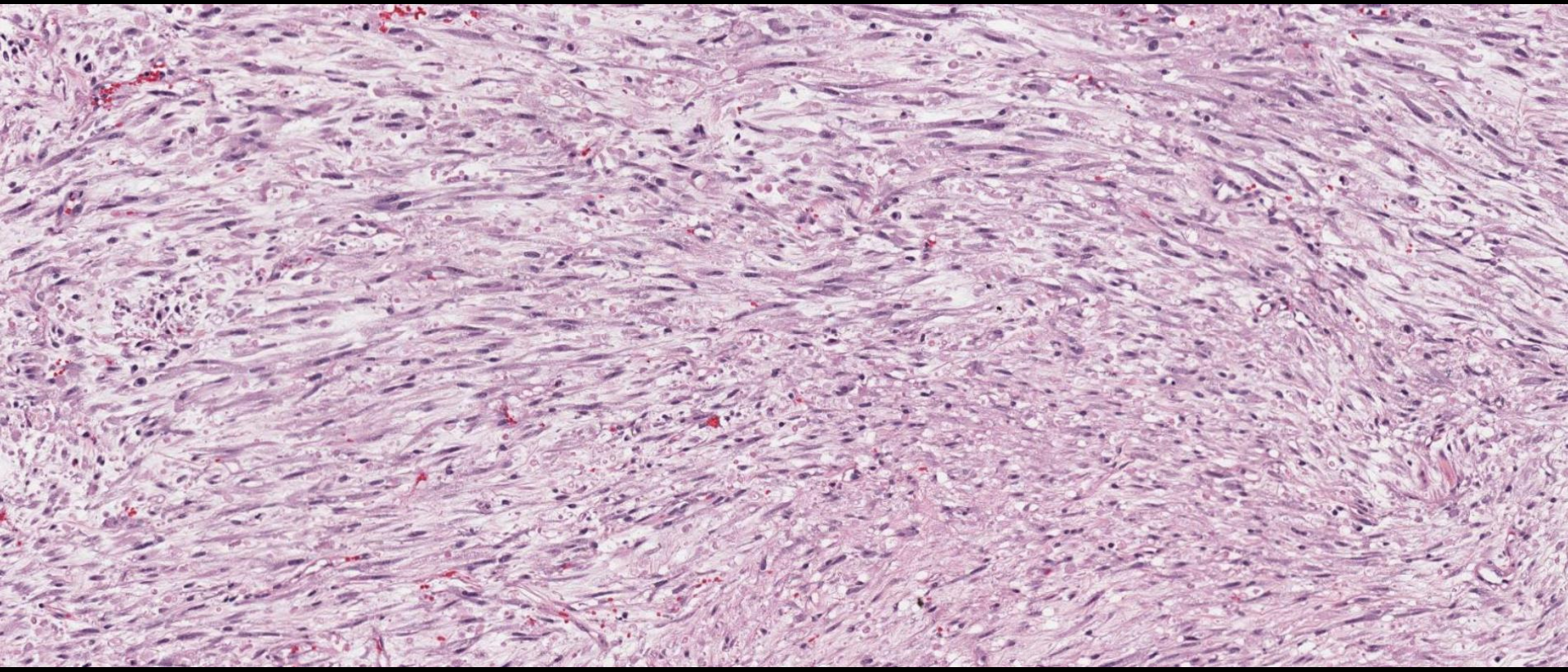

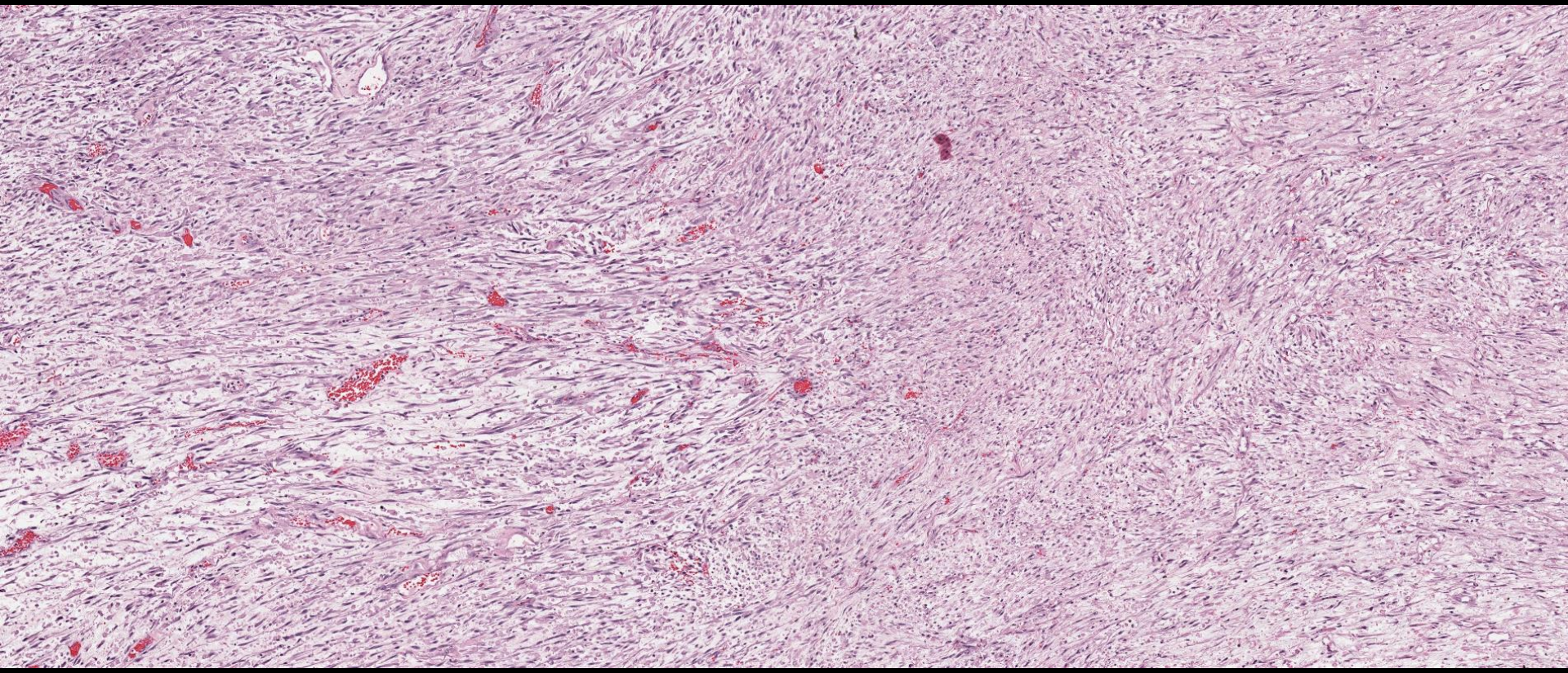

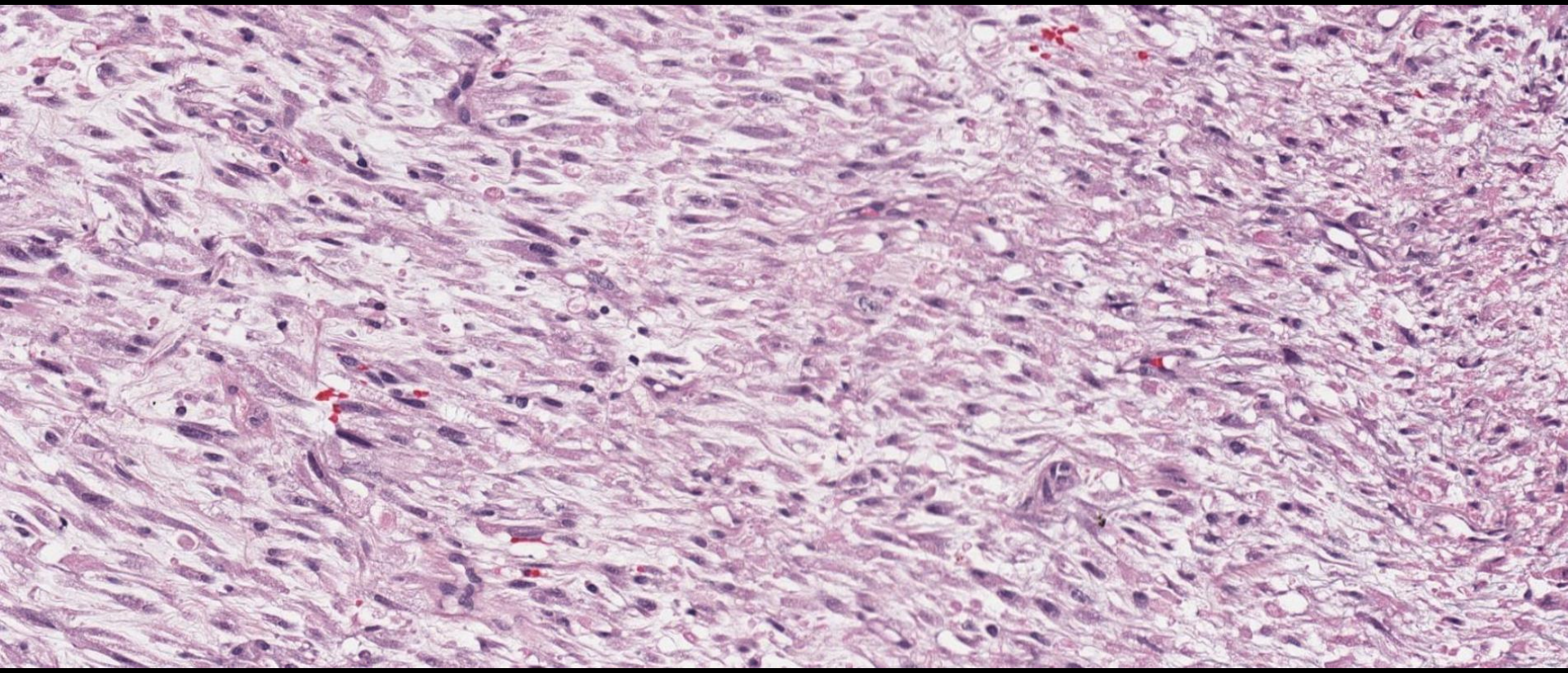

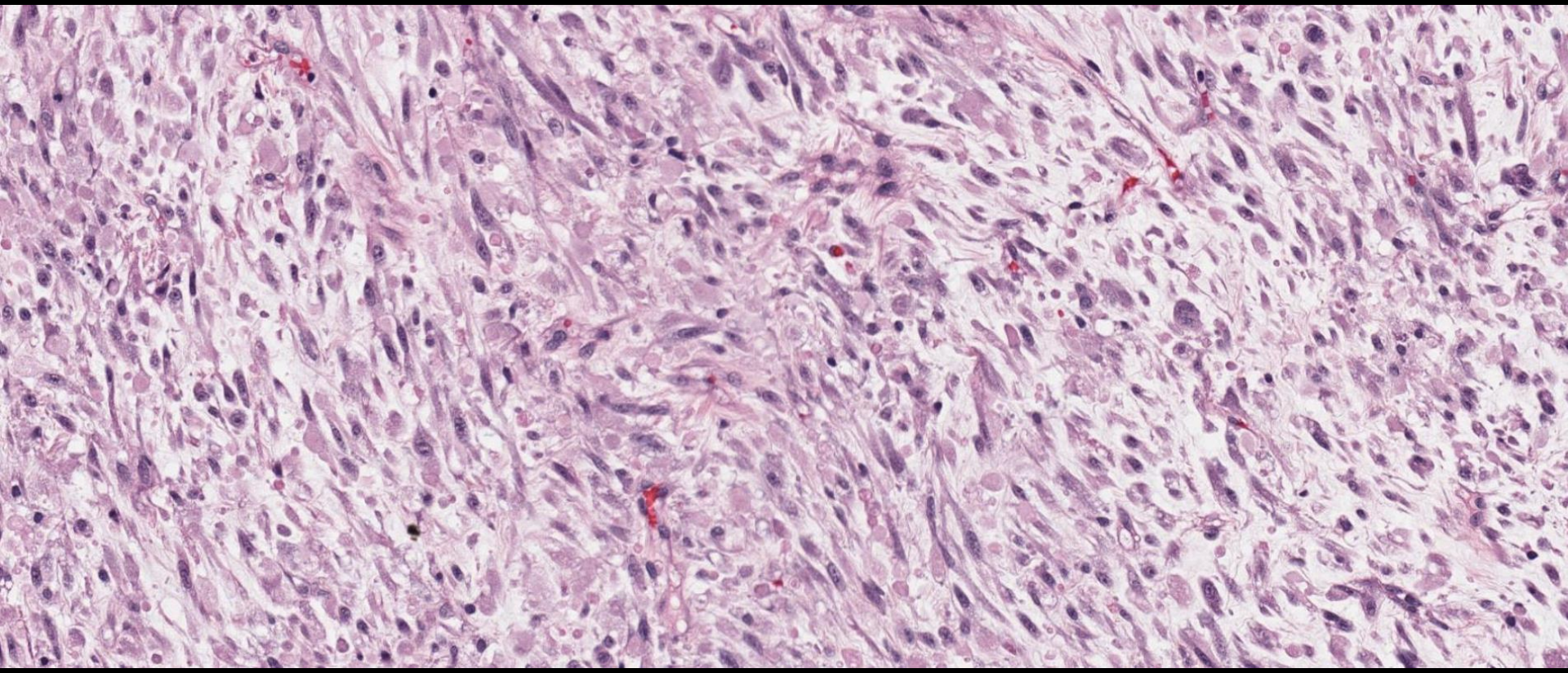

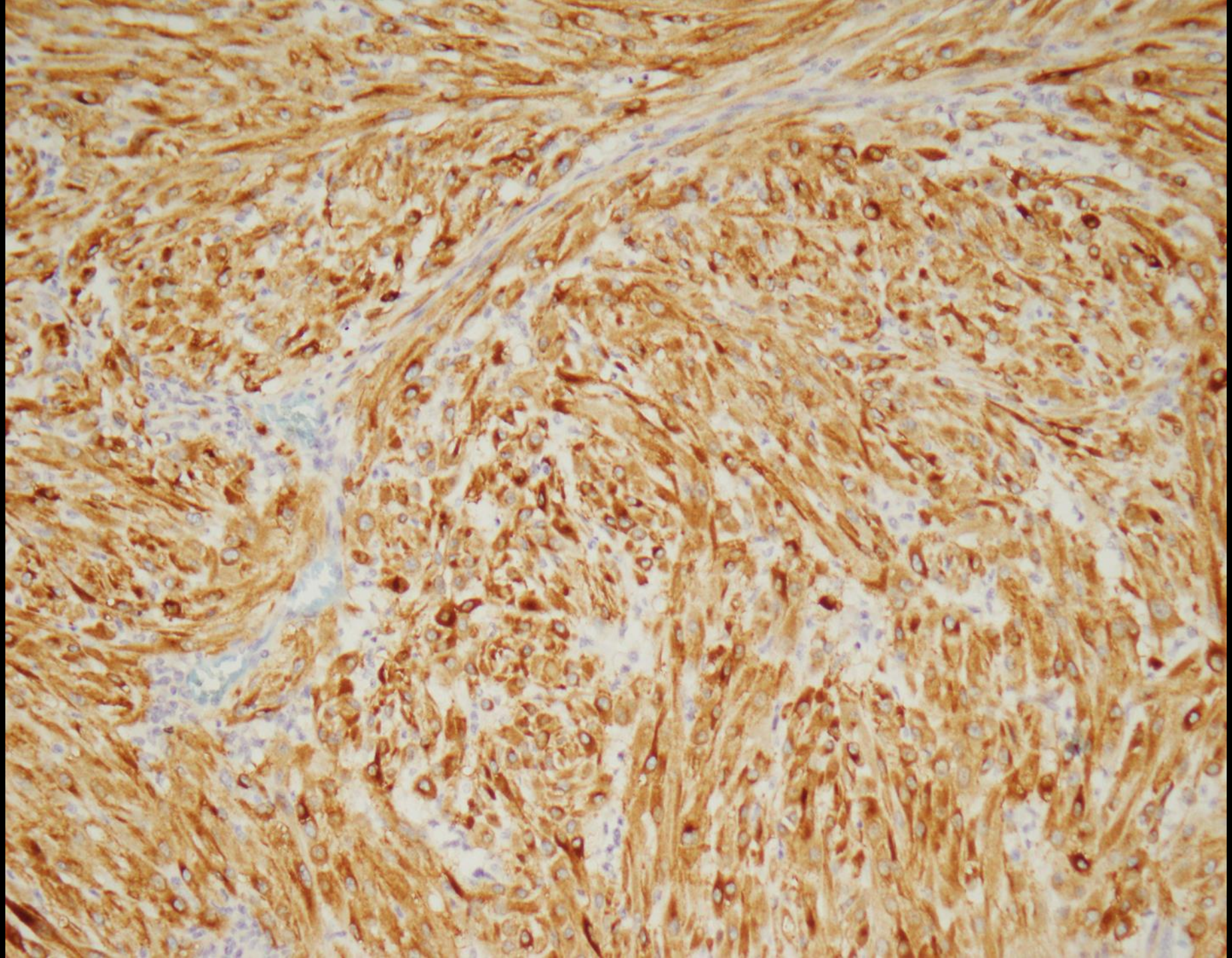

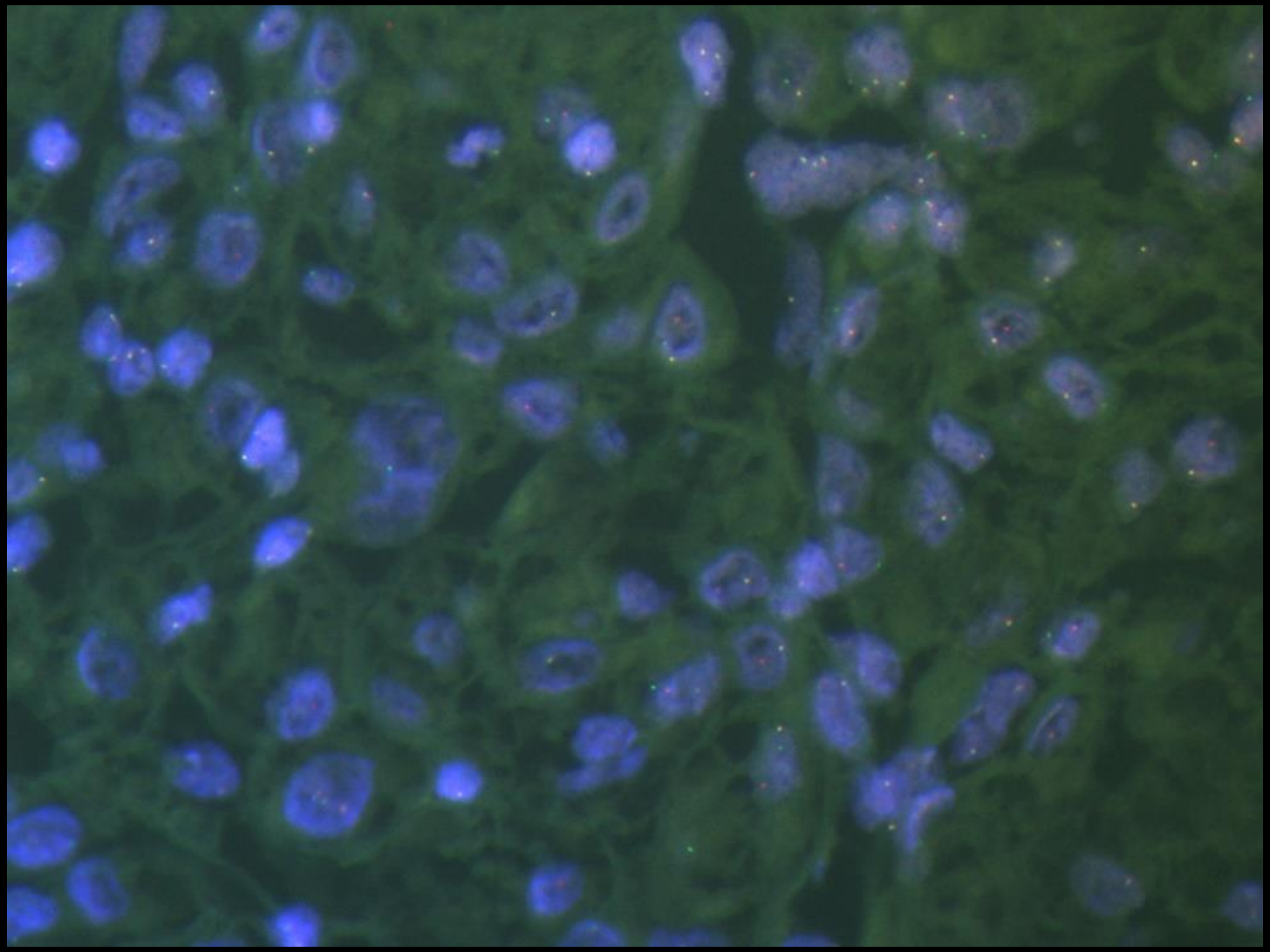

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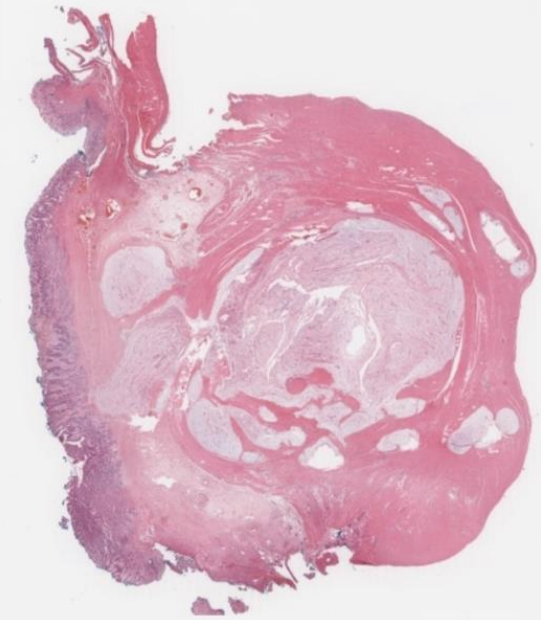
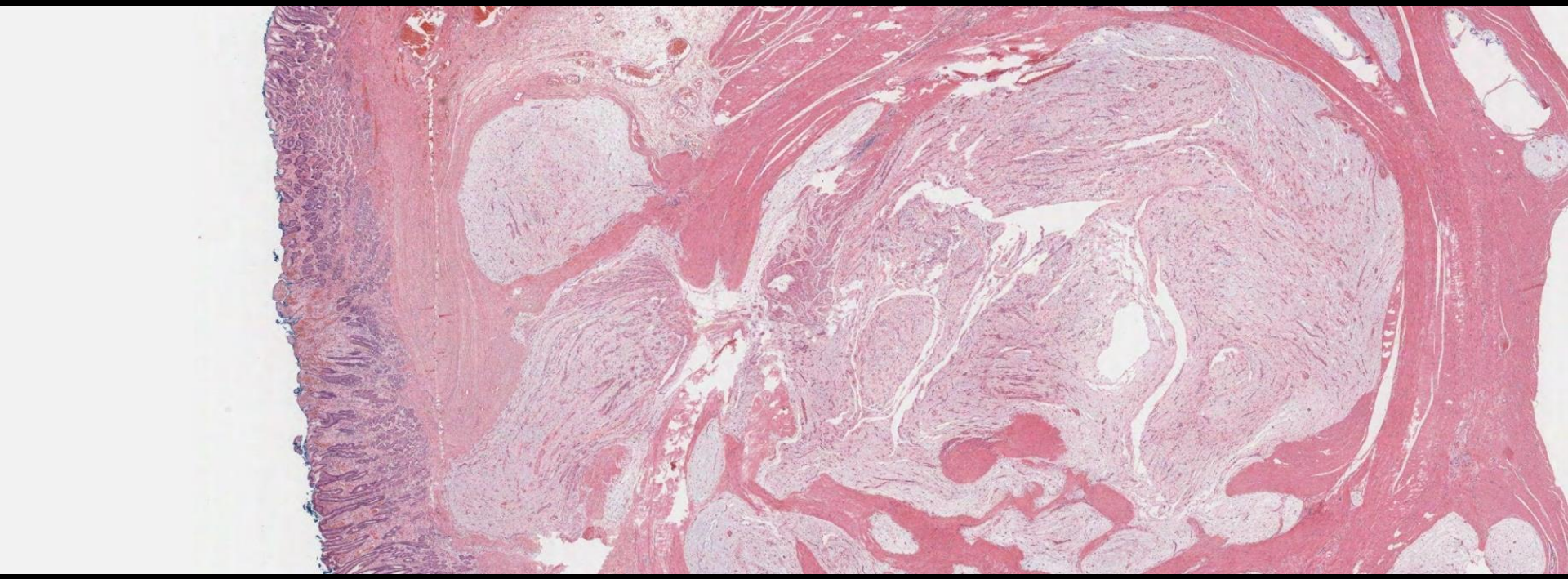
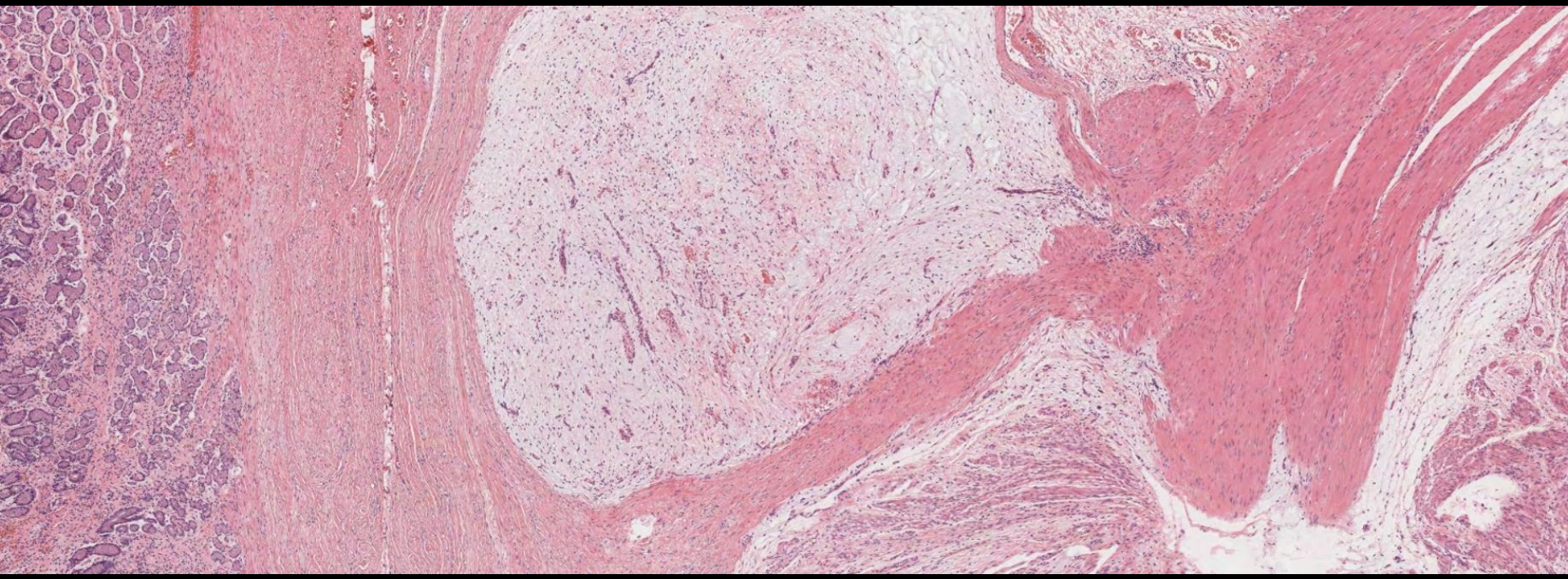




RCPA QAP slide set



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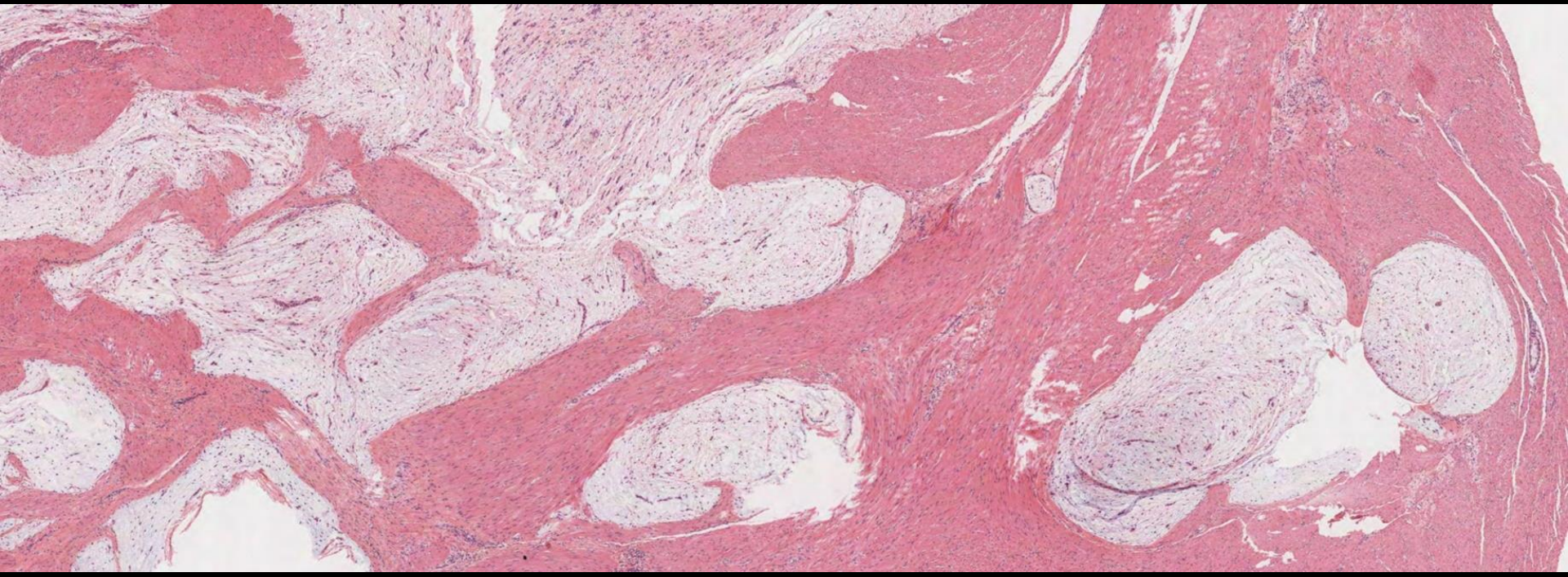

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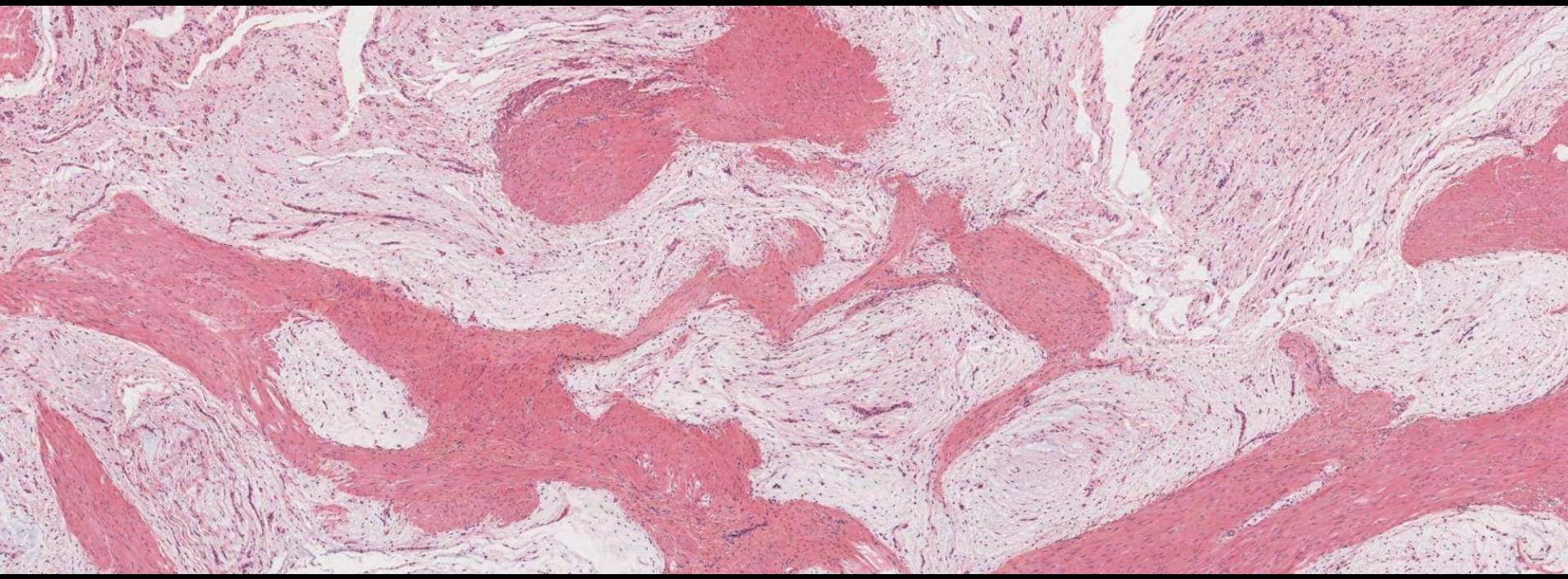

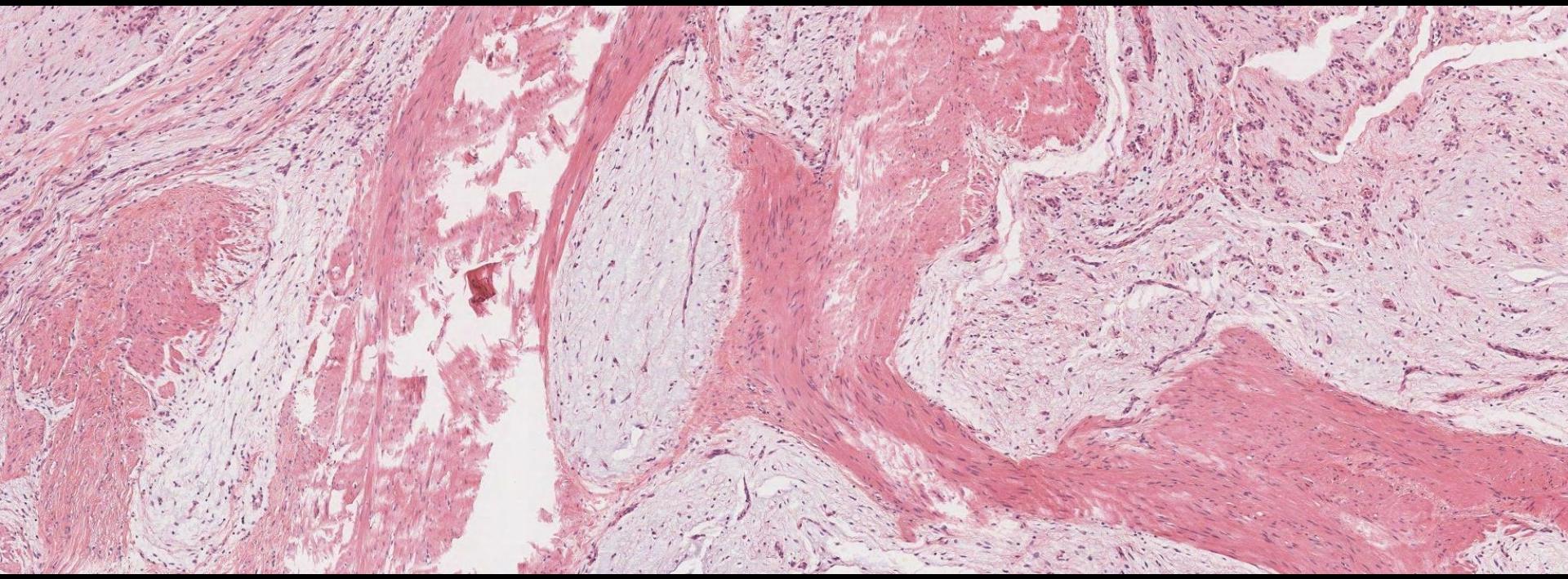

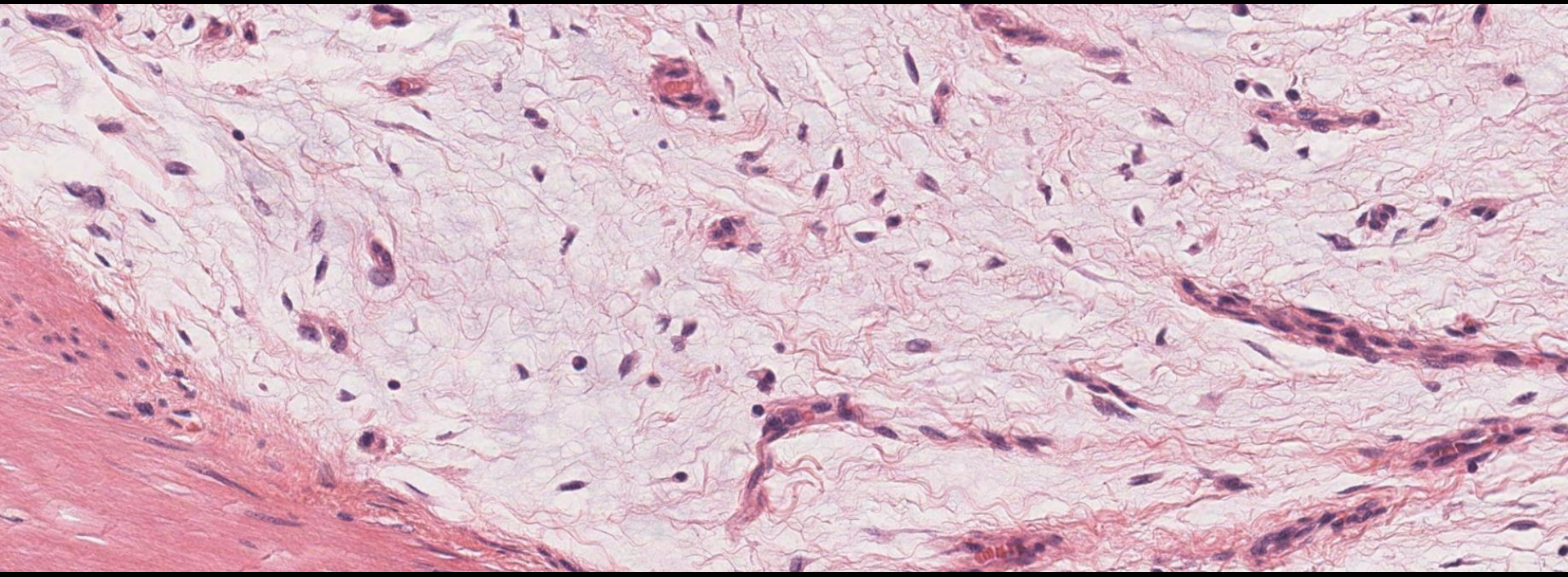

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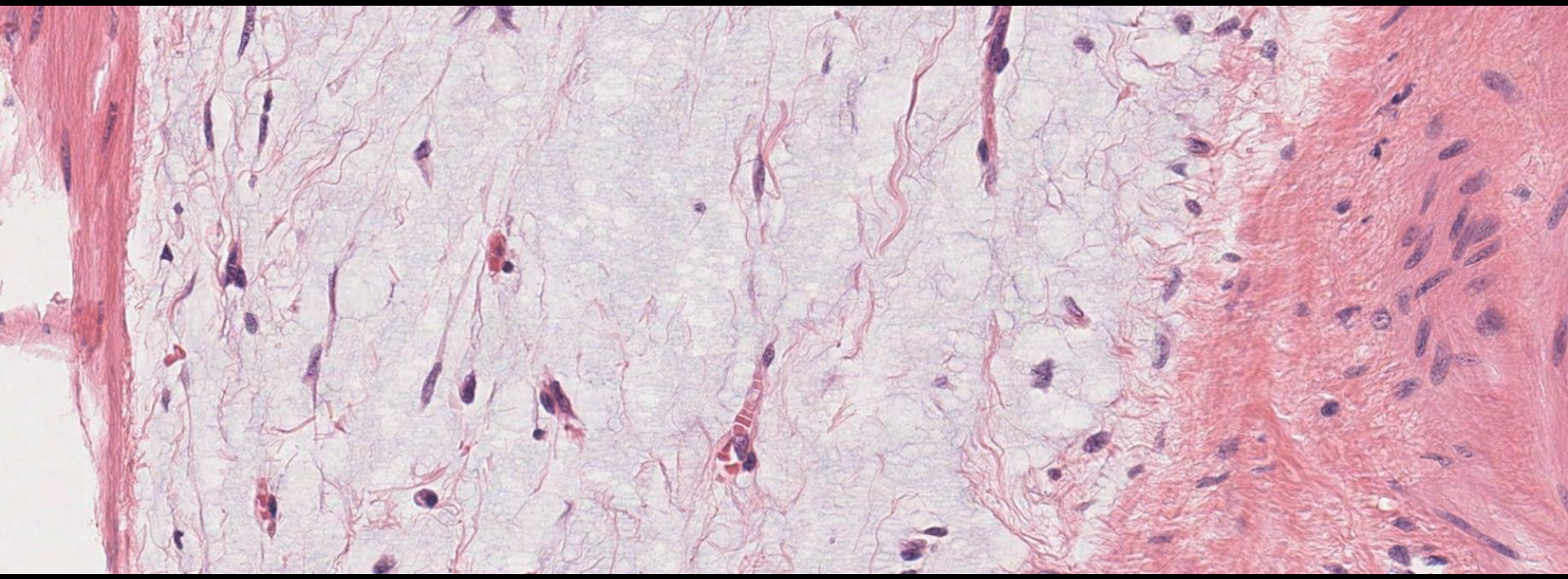

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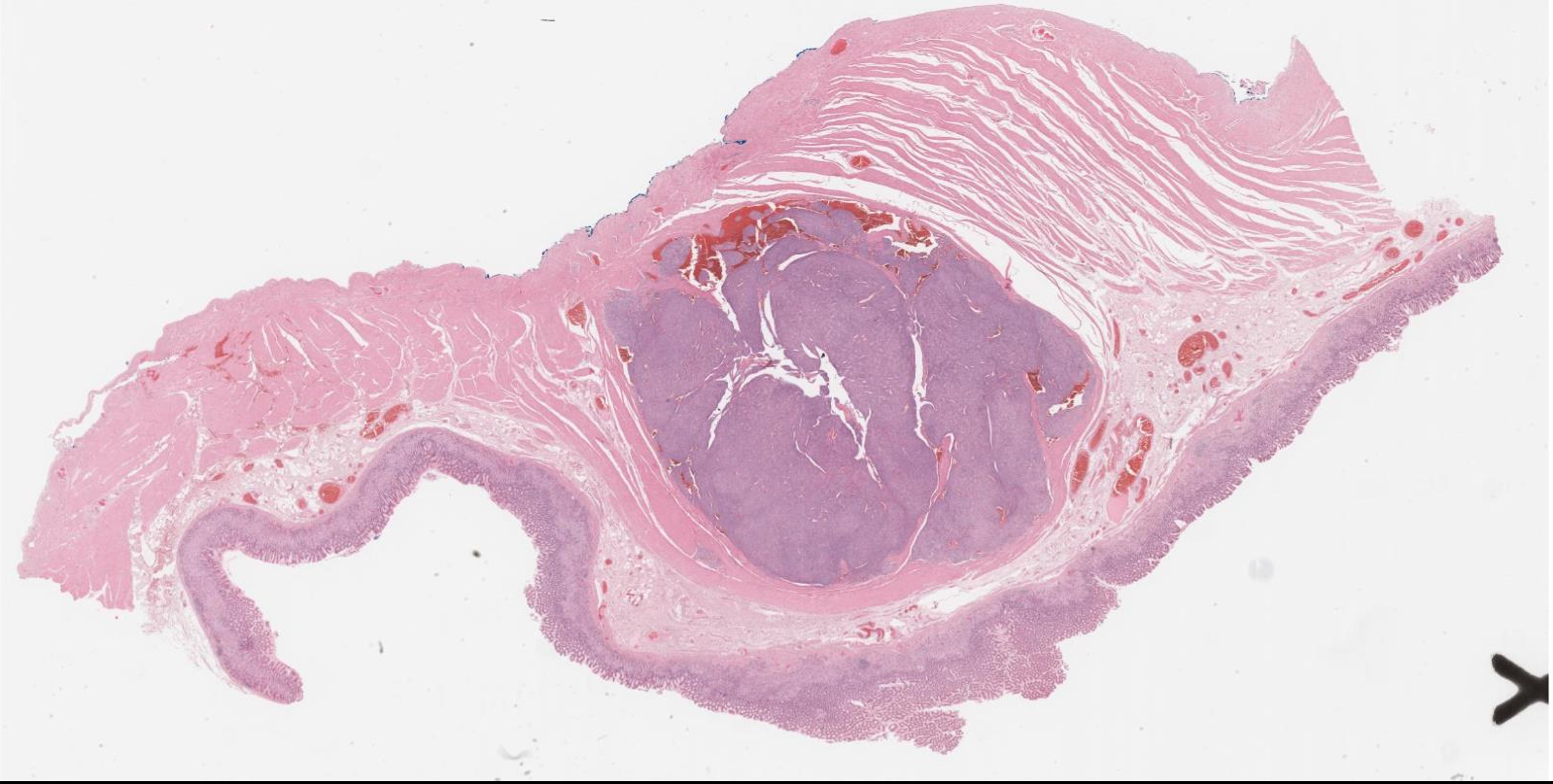

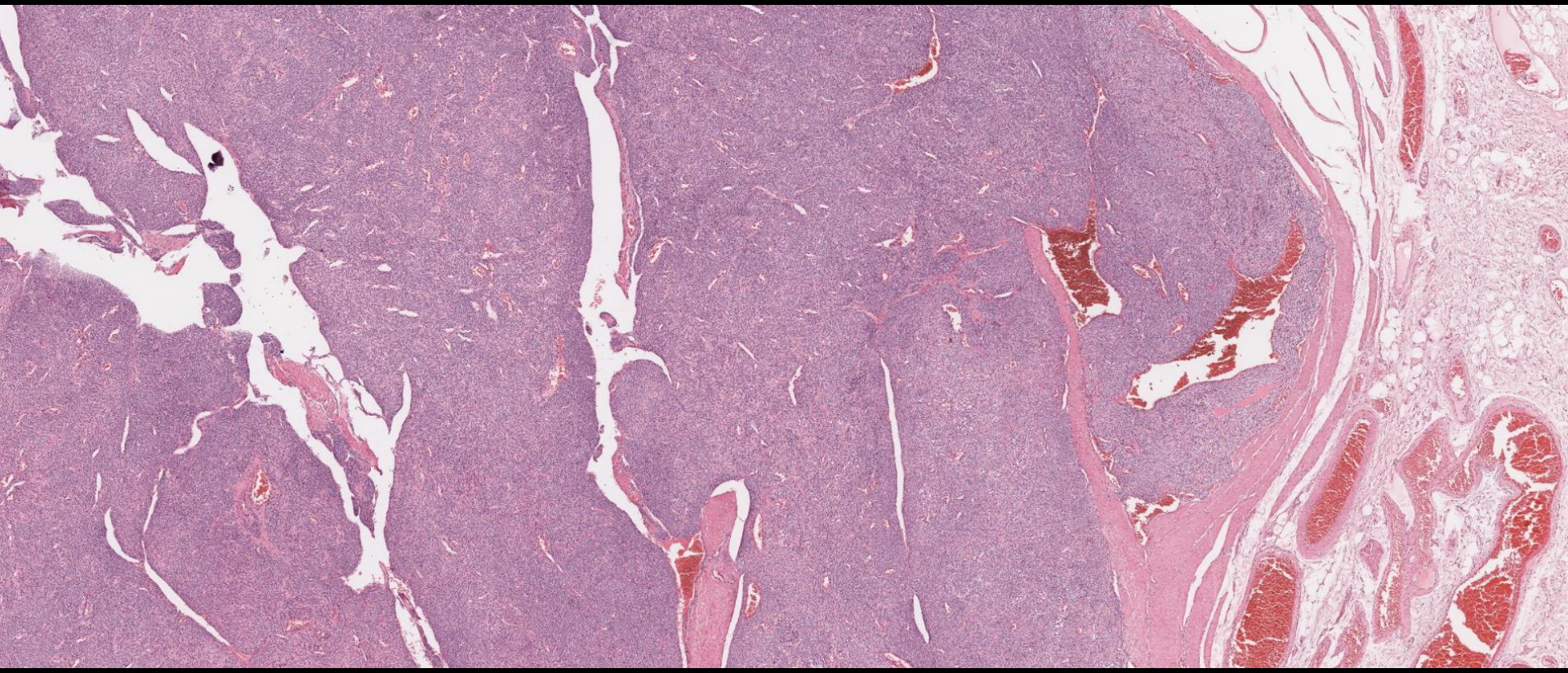

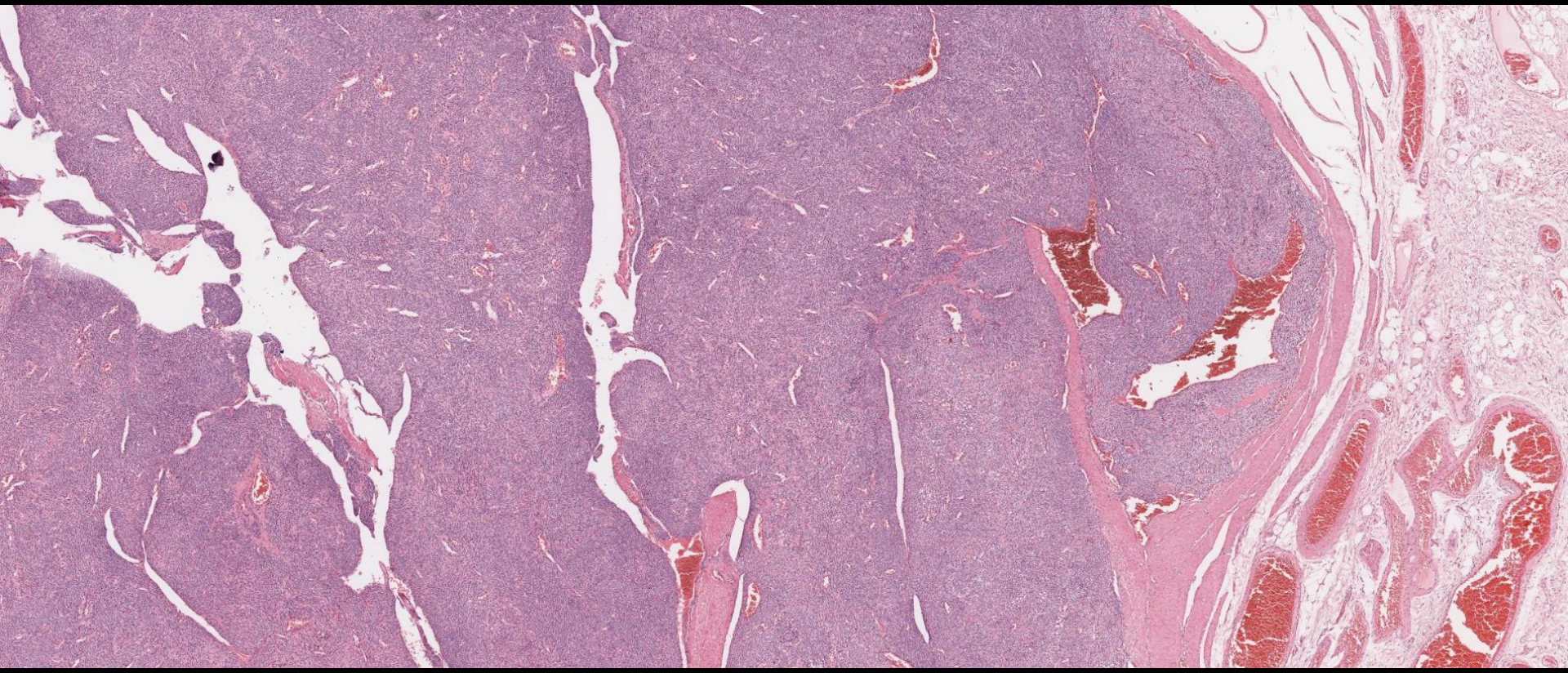

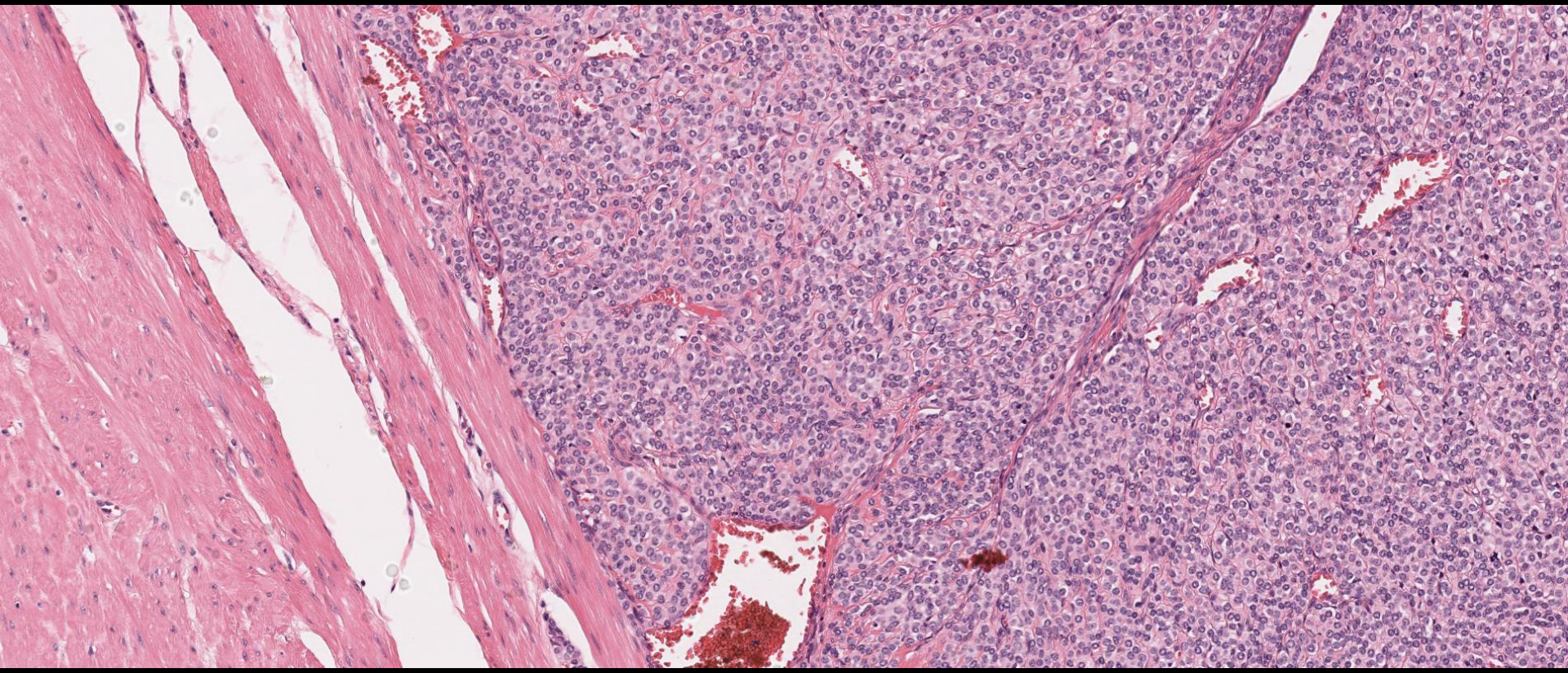

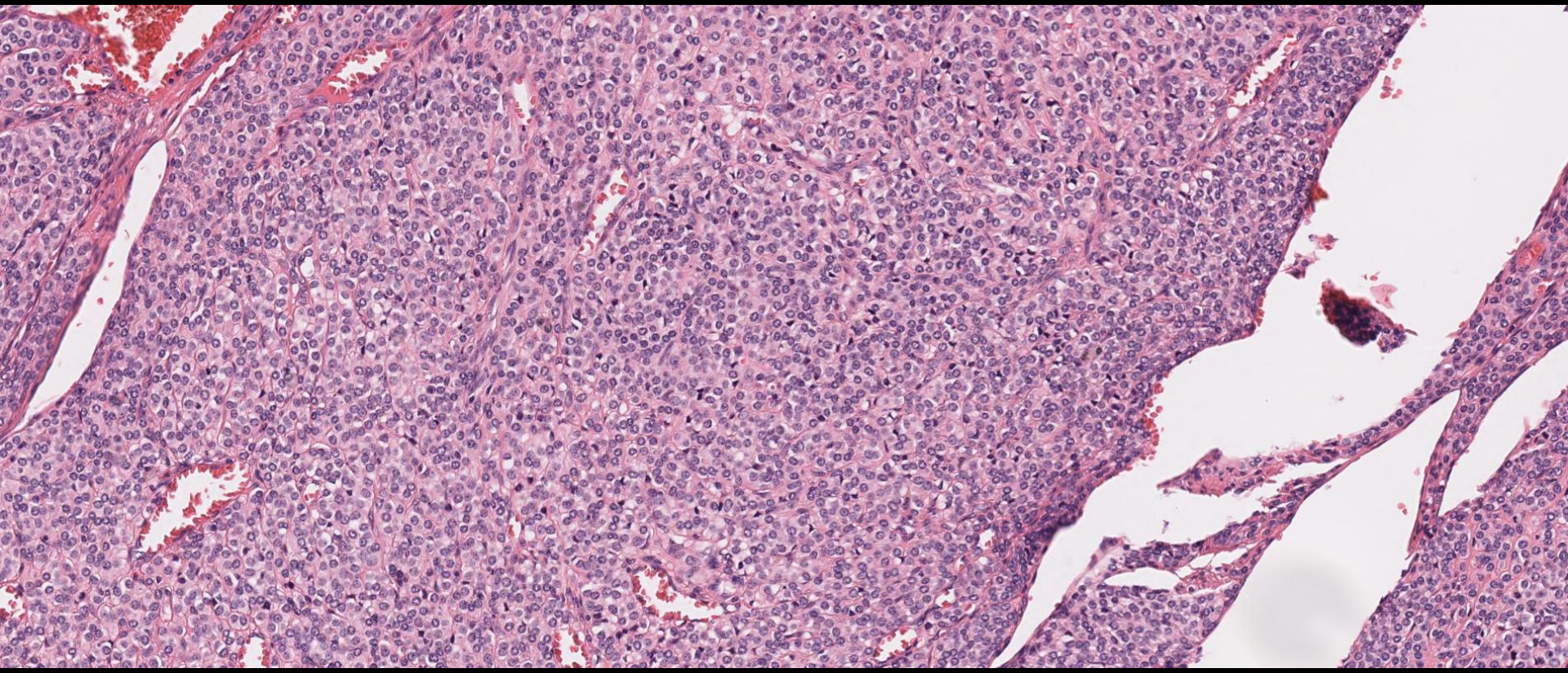

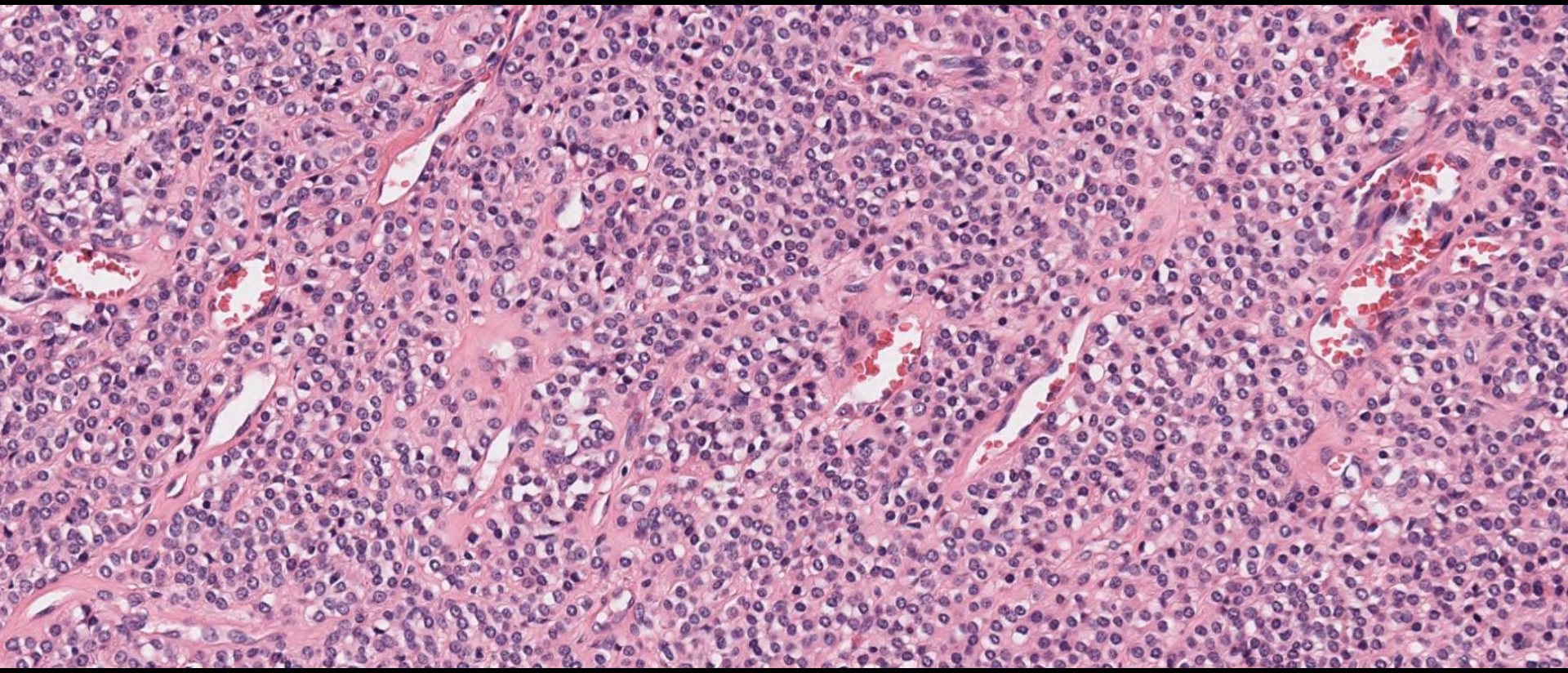

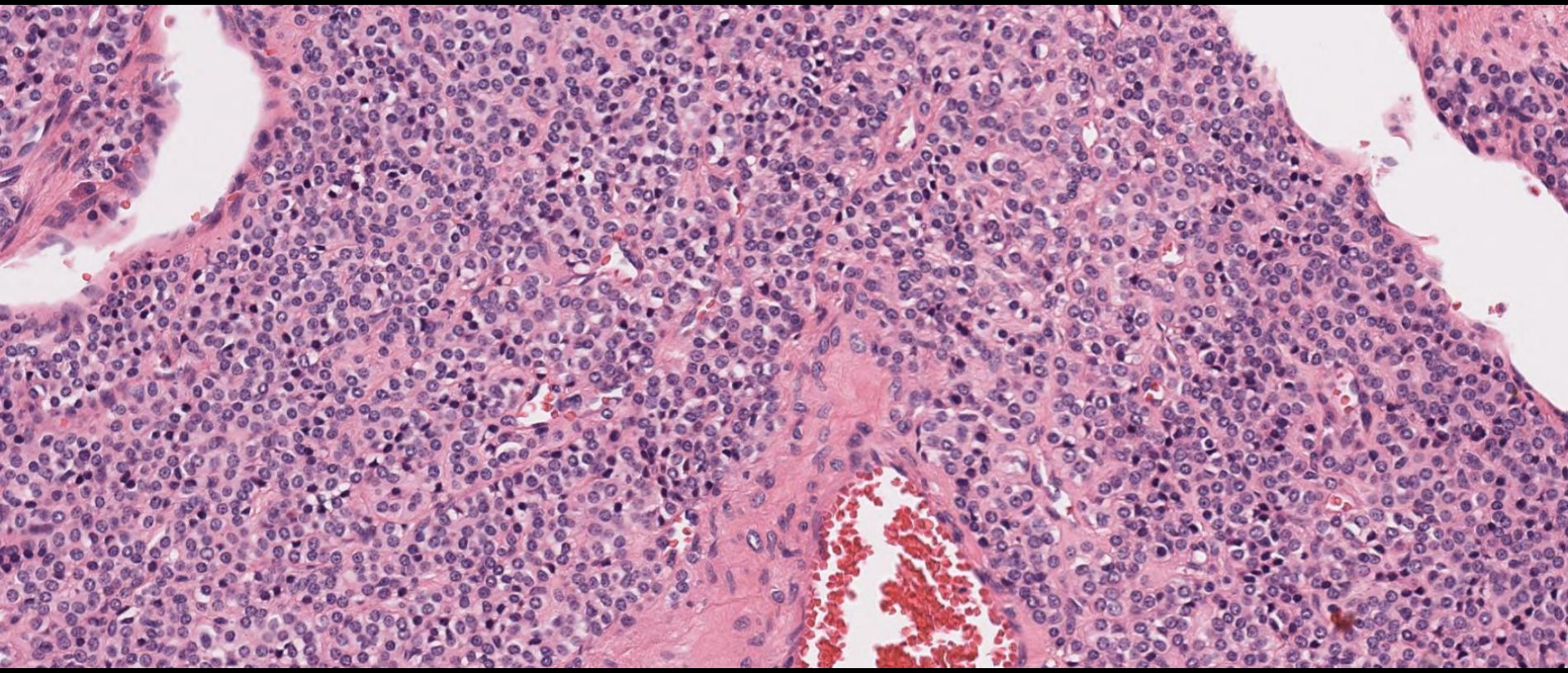

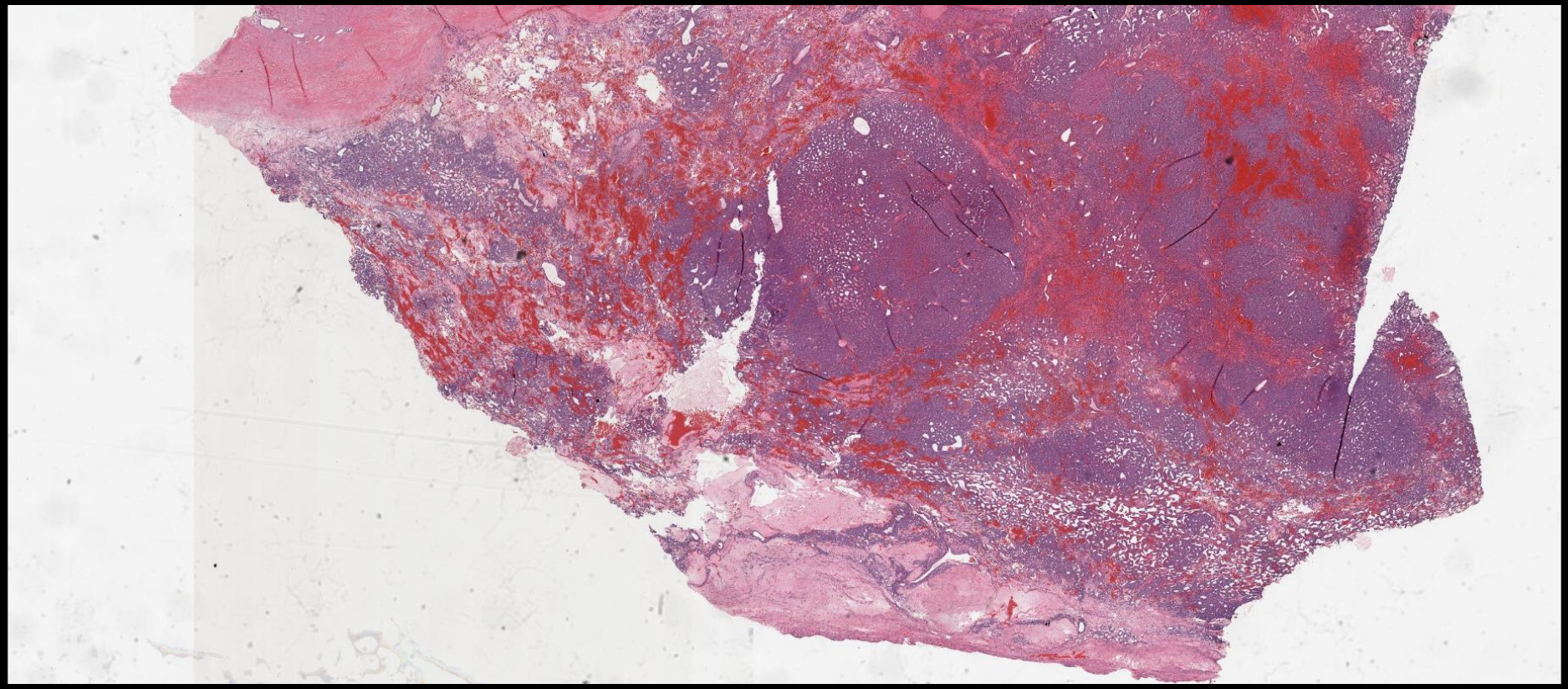

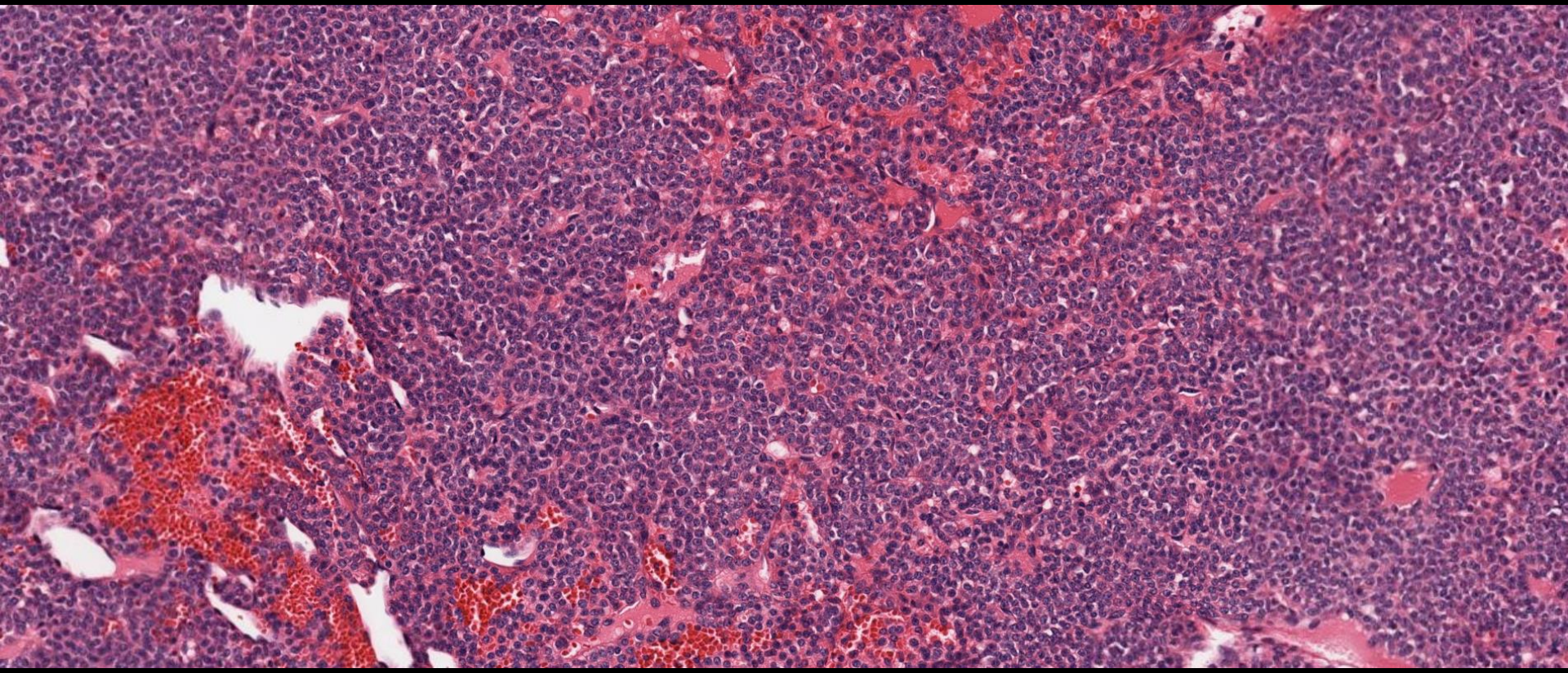

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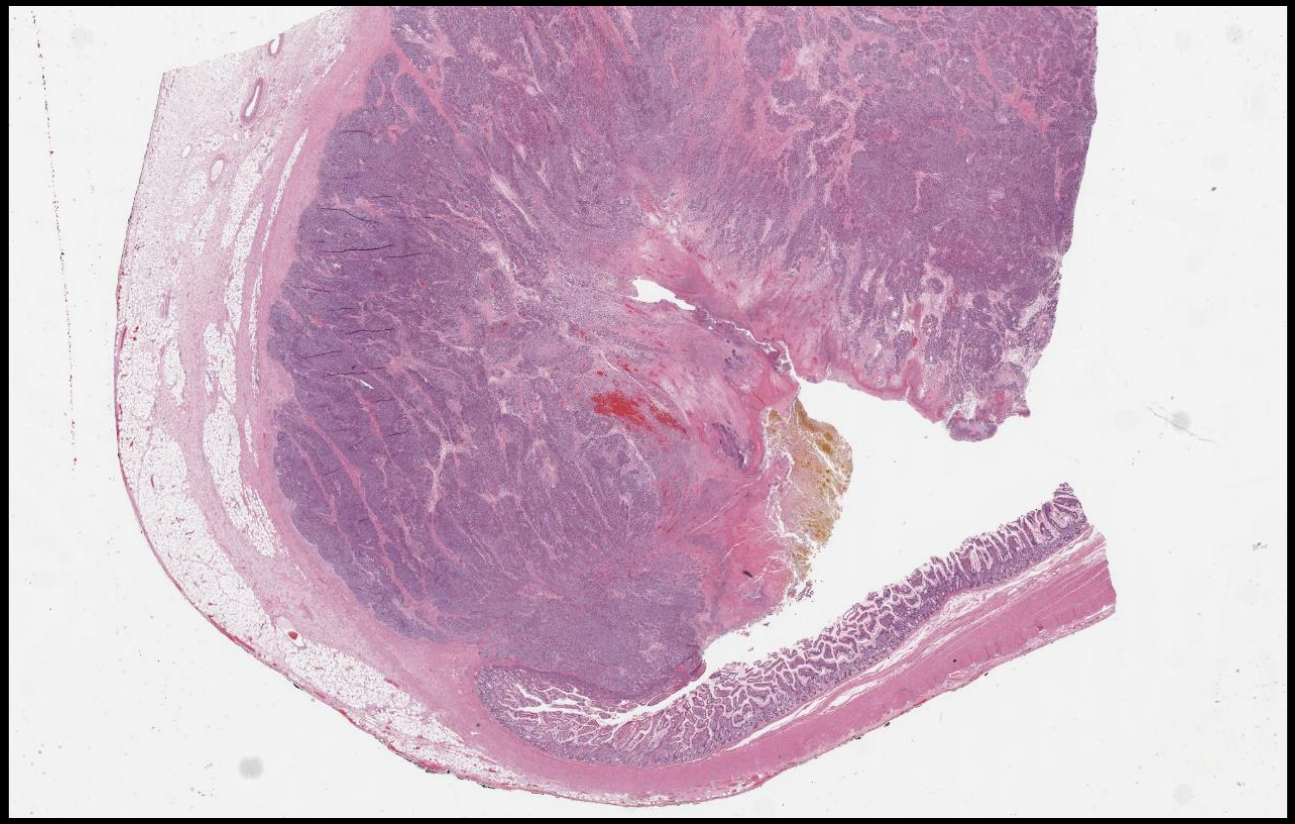

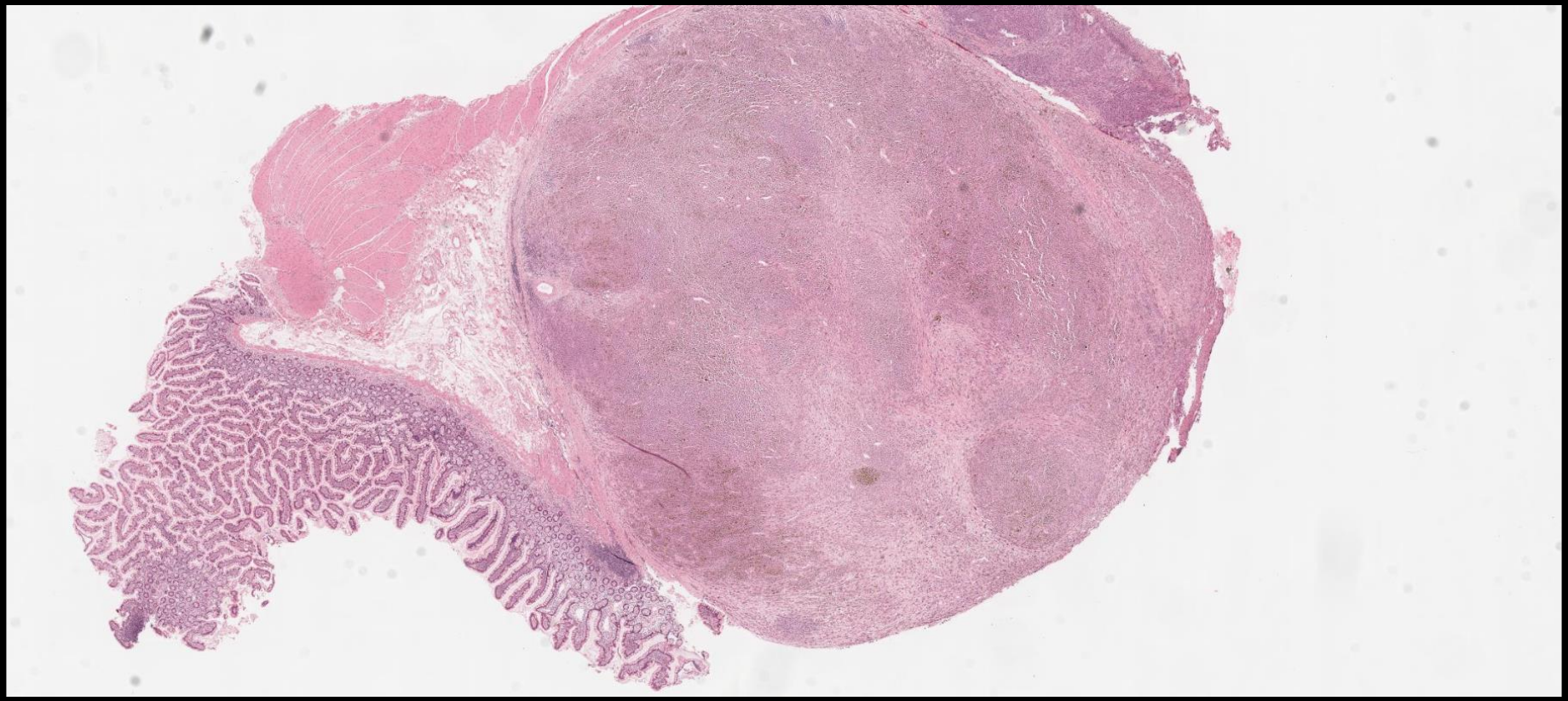

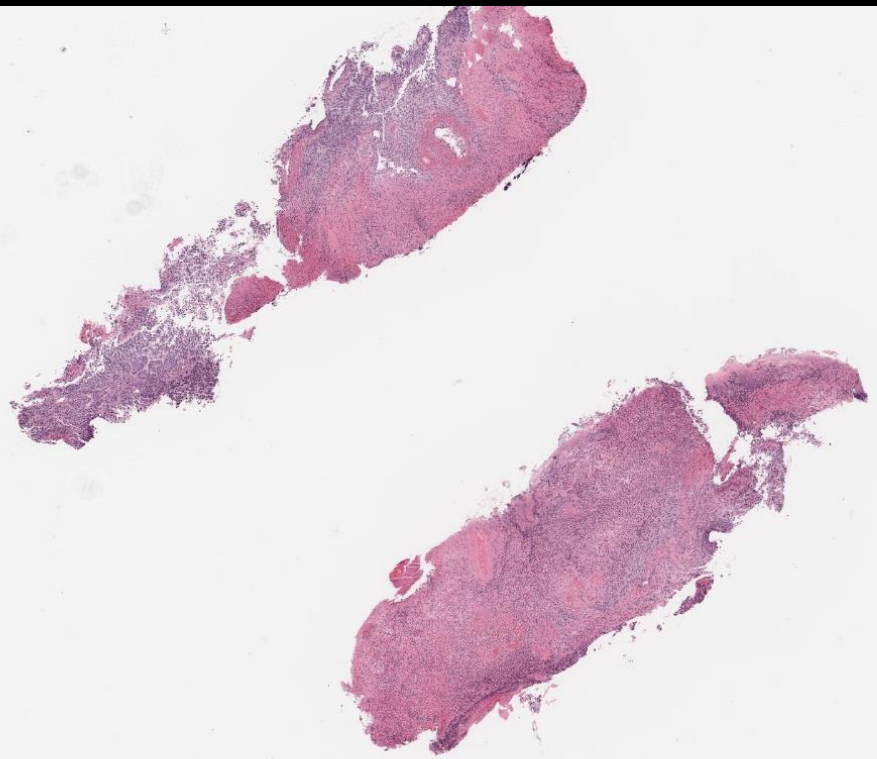

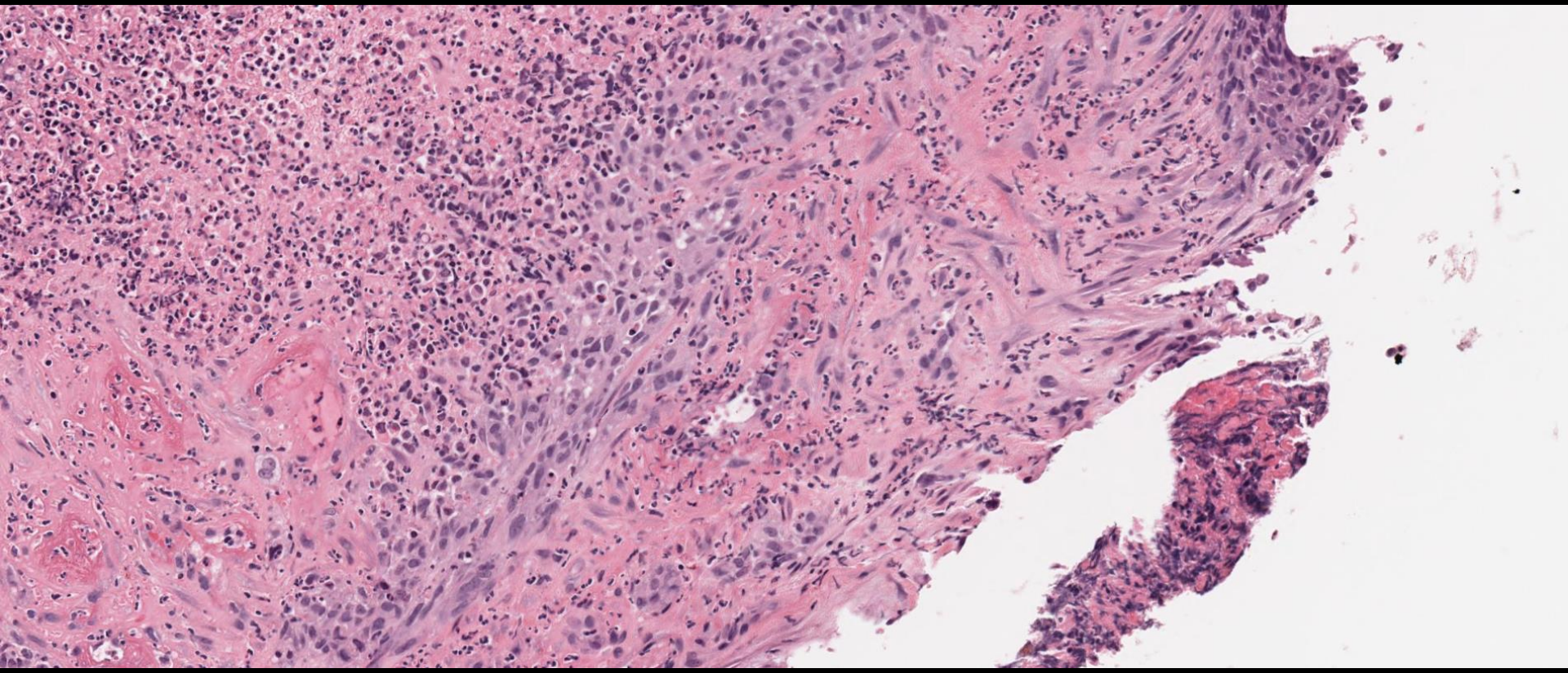

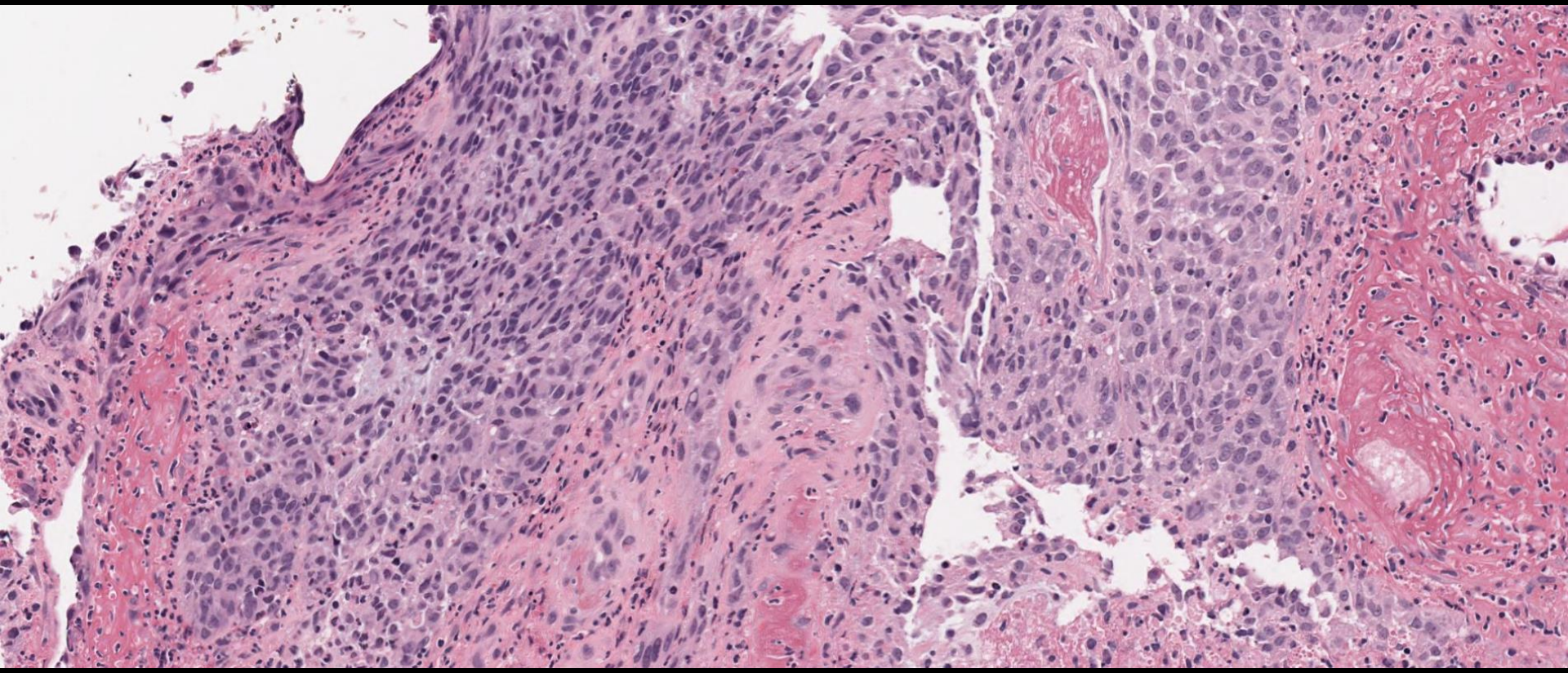

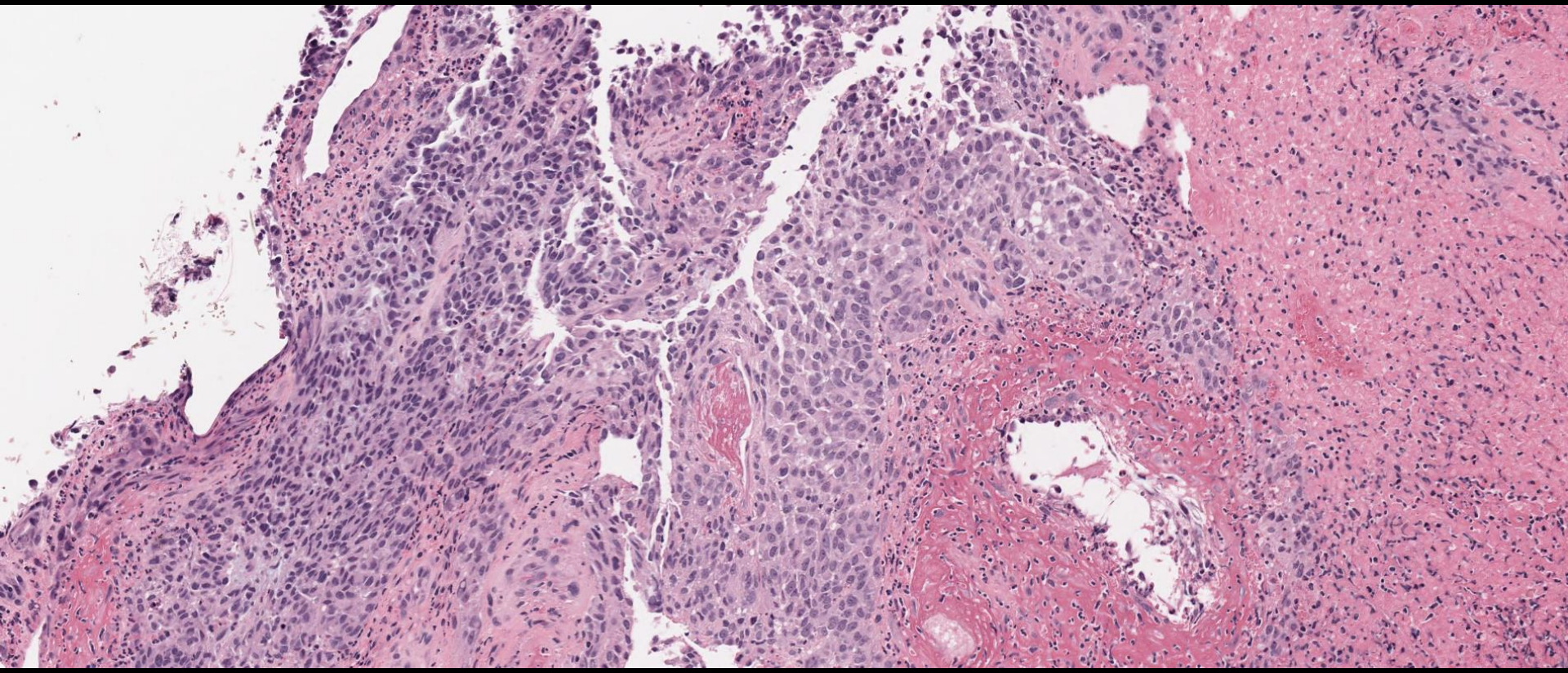

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SUMARY

If targeted therapy for GIST is being considered (or when secondary resistance occurs) all GISTs ***SHOULD*** be tested for:

cKIT exons 9, 11, 13, 17

PDGFRa exons 18,12,14

WILD TYPE now means at least QUADRUPLE WILD TYPE (KIT, PDGFRA, SDH, BRAF, NF1, RAS)

WILD TYPE GISTS may be associated with NF1

Impress people by identifying PDGFRA mutant GIST by location and morphology

SDH deficient GISTs are unique

WHO 2018

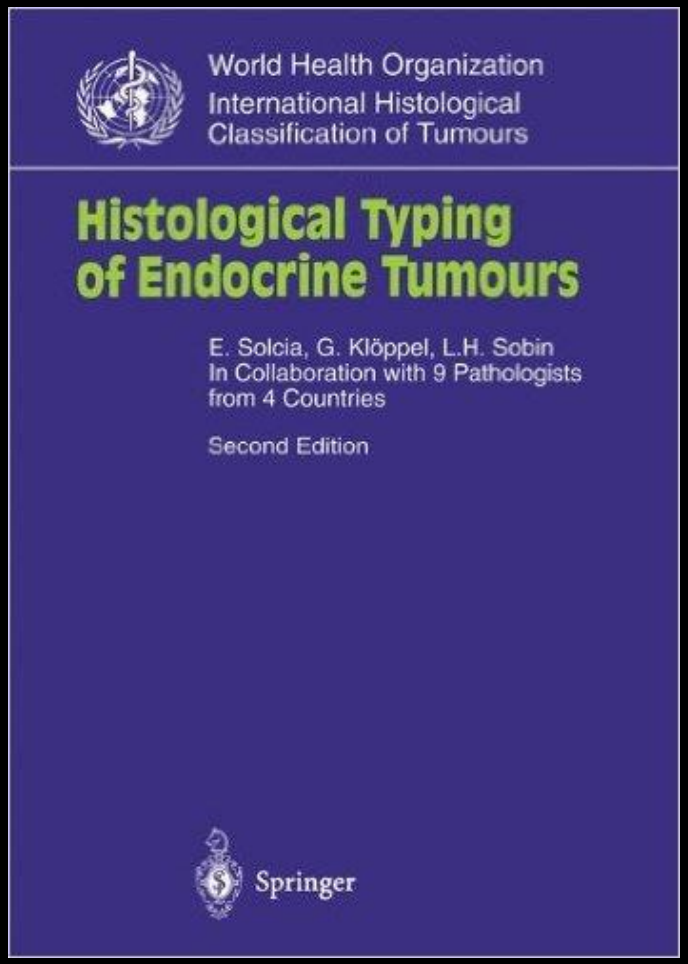
Update in NETs grading

An update from the new WHO classification

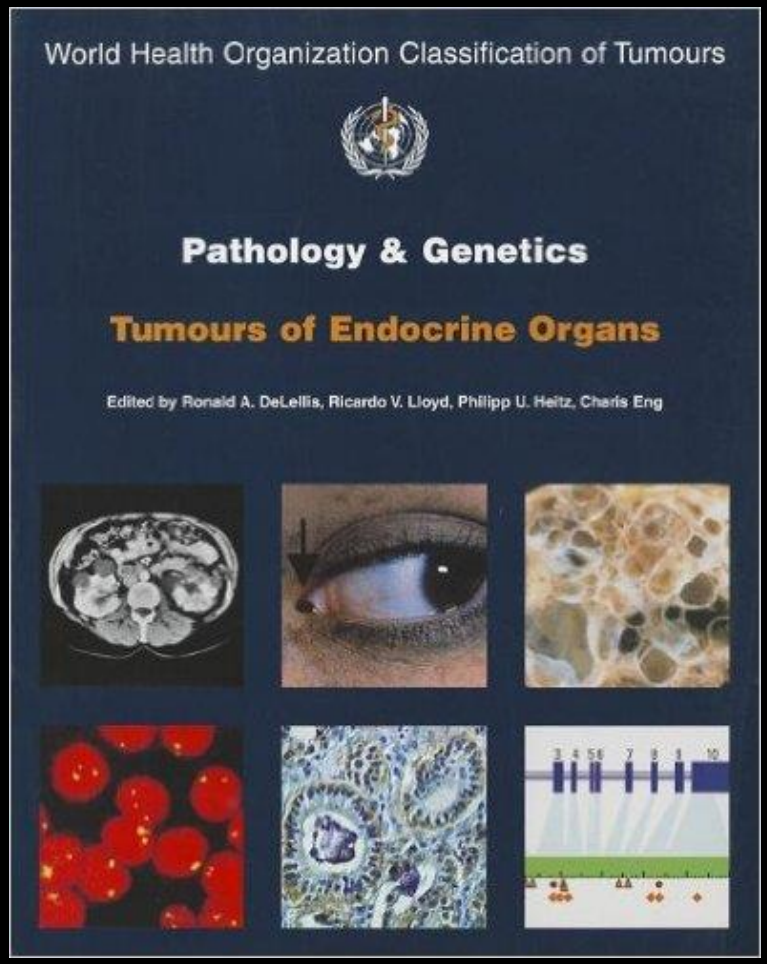
5th Edition 2018

Anthony J Gill MD FRCPA
Royal North Shore Hospital
Professor of Surgical Pathology
University of Sydney

@CaDxPath



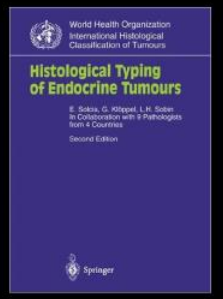
2nd Edition



3rd Edition

History of the WHO Classification

- 1956 – WHO executive board initiates project
- 1967-1981 – First Edition Published
  - Simple format – lists terms with ICD codes
  - Very brief description of histologic criteria
- 1982-2002 – Second Edition Published
  - Simple format
  - Histology complemented by list of IHC markers
  - Each tumour type had at least one Photograph
- 2000-2005 – Third Edition Published
  - Transformation in content in layout/content
- 2006- Fourth Edition Published



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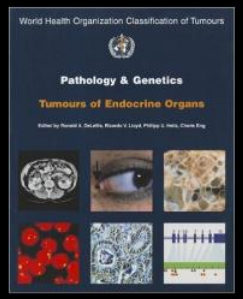

3rd Edition

5th Edition WHO Series

- Standing Editorial Board
- Specialist Editorial Board
- Authors selected -> based primarily on a publication algorithm


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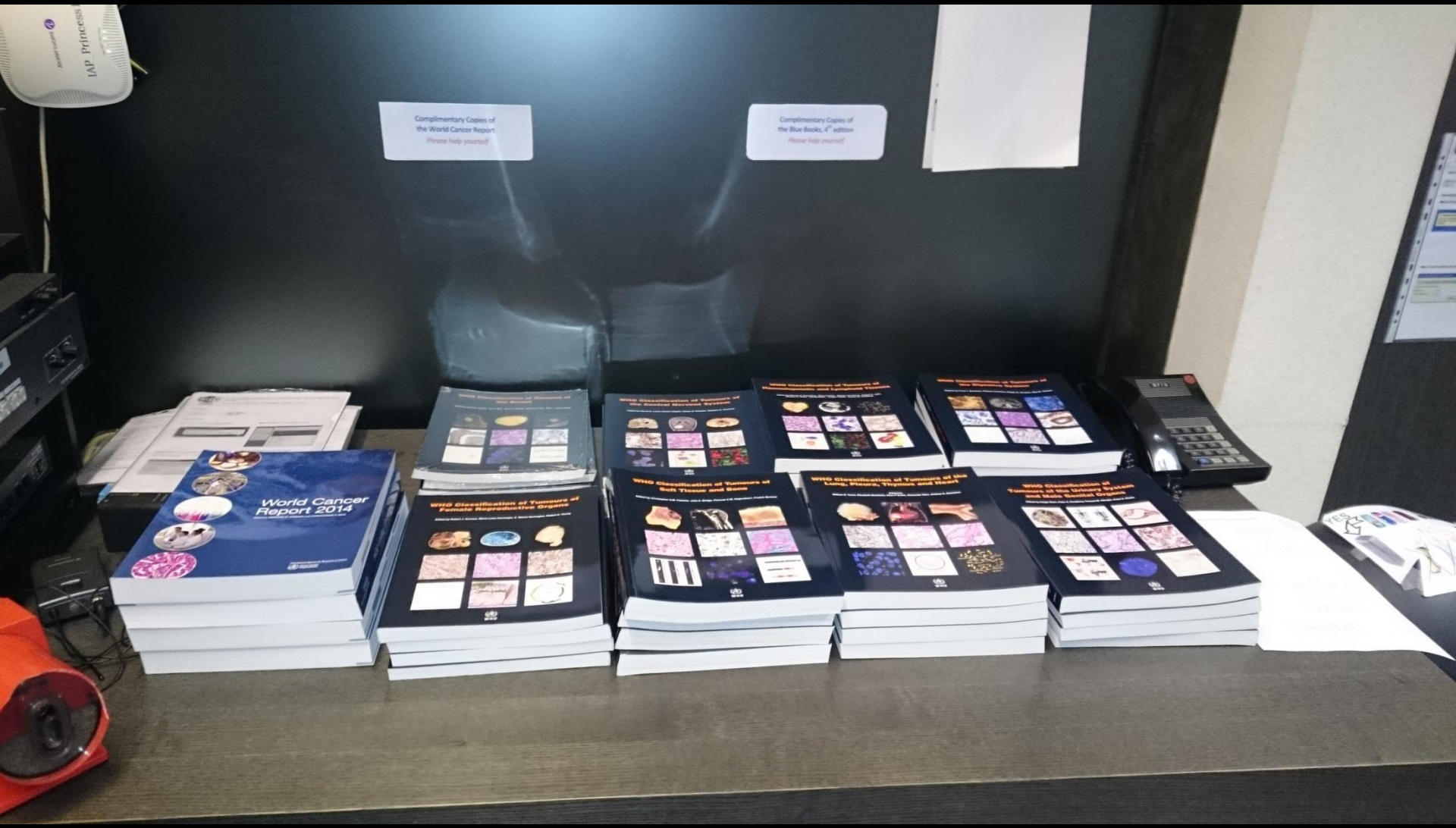
OMS
WHO
CIRC
Centre International de
Recherche sur le Cancer
IARC
International Agency for
Research on Cancer


Complimentary Copies of
the World Cancer Report
Please help yourself
Complimentary Copies of
the Blue Books, 4th edition
Please help yourself
World Cancer
Report 2014
WHO Classification of Tumours of
Female Reproductive Organs
WHO Classification of Tumours of
Soft Tissue and Bone
WHO Classification of Tumours of the
Lung, Pleura, Thymus and Heart

WHO 2010 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	≤ 2 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3*	>20 %	>20/10 HPF
Mixed adenoneuroendocrine carcinoma (MANEC)		

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

WHO 2017 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs		**Mitotic index**
Neuroendocrine tumour (NET) G1	3%	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20%	>20/10 HPF
POORLY DIFFERENTIATED NENs		
Neuroendocrine Carcinoma (NEC) G3	>20%	>20/10 HPF

MENEN (mixed endocrine neuroendocrine carcinoma)

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

G3 NETS vs G3 NECs

Low grade NETs	**Poorly Diff NECs**
MEN1, DAX, ATRX mutations	P53, RB1 mutations
Recognisable as NETS	Small cell or large cell type
Often evolve from a recognisable lower grade component	No lower grade component
No upper limit given, but usually ki67 <40 to 55%, mitotic count <20/10hpf	Must have ki67 index >20%, no lower limit given but usually >55%

WHO 2017 Grading System

TABLE 1

World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index*|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
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Small cell type		
Large cell type		

Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)

* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.

The changes for fifth edition GIT blue book

WHO 2017 Grading System

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??WHO 2018/19 Grading System for NETs

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Towards a uniform grading system for all NENs

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https://doi.org/10.1038/s41379-018-0110-y

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Methods

A dedicated consensus meeting was held in Lyon on 2–3 November 2017 at IARC, under the auspices of the WHO

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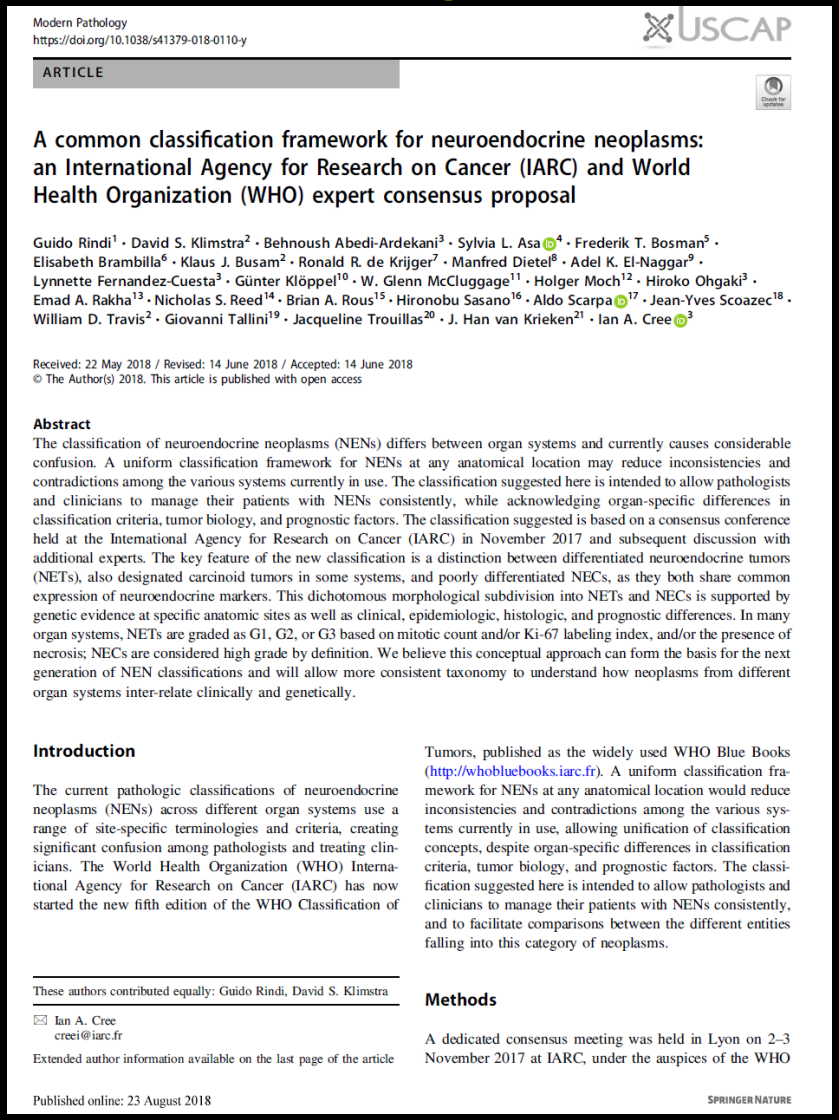
November 2017 Consensus

Towards a uniform grading system for all NENs



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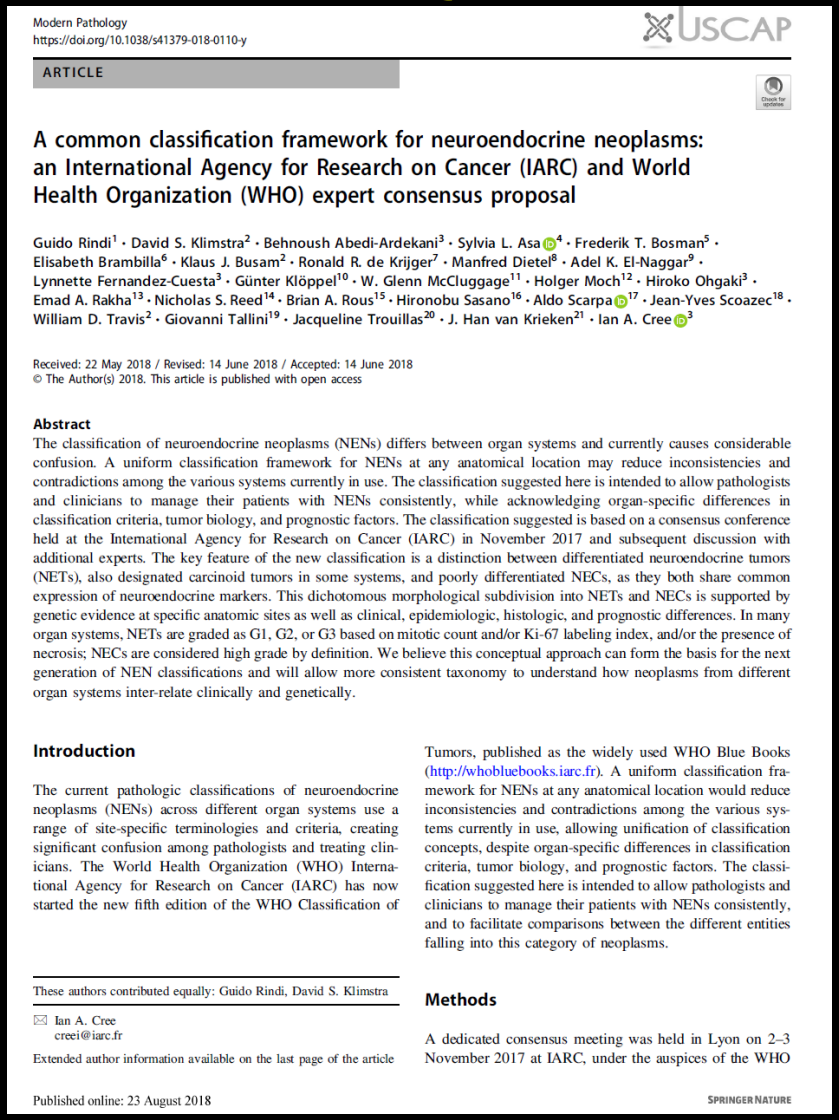
SPRINGER NATURE

November 2017 Consensus

Key Features:

Clear distinction between NET and NEC

Towards a uniform grading system for all NENs



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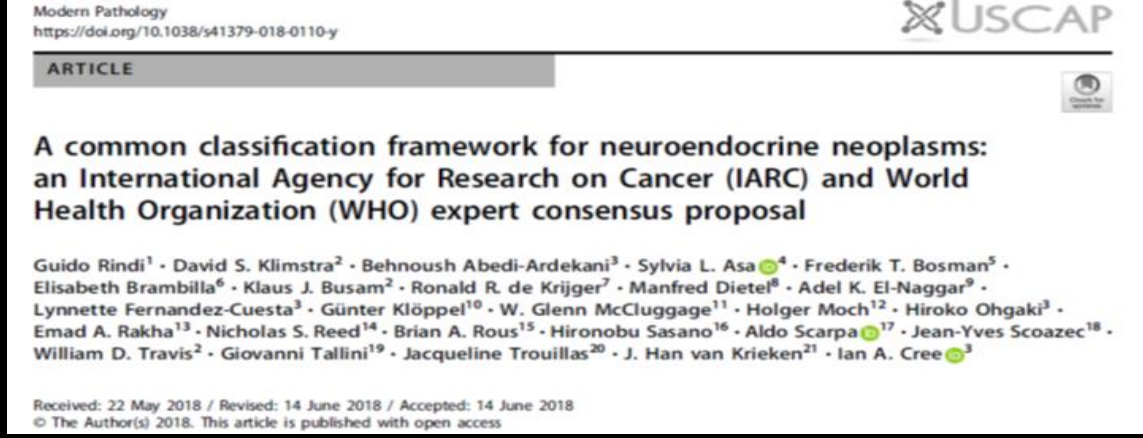
SPRINGER NATURE

November 2017 Consensus

Key Features:

Until the new WHO system is in place for each tumour type, pathologists *'should'* use the old scheme

General Considerations



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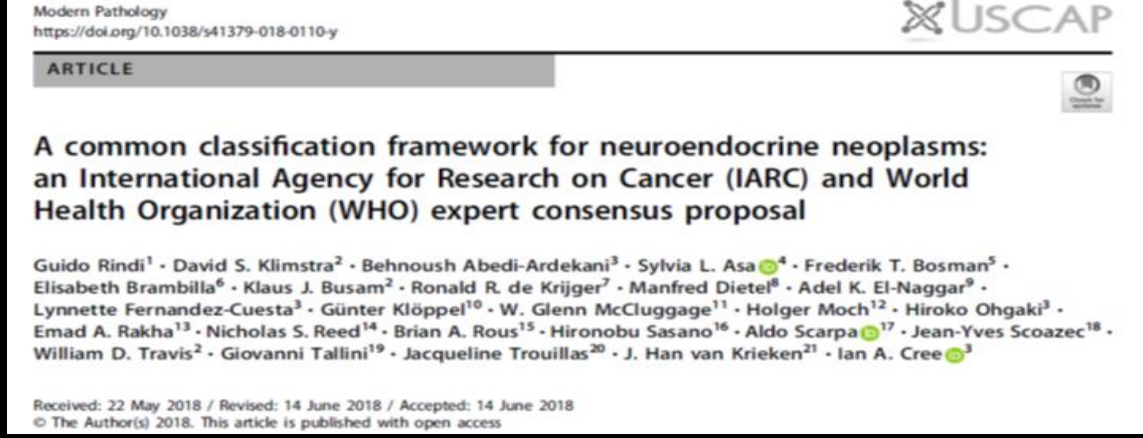
Existing systems vary widely in terminology

Robust data for some sites (lung, GIT, Pancreas)

Poor data for other sites (breast, thyroid, parathyroid)

General Considerations



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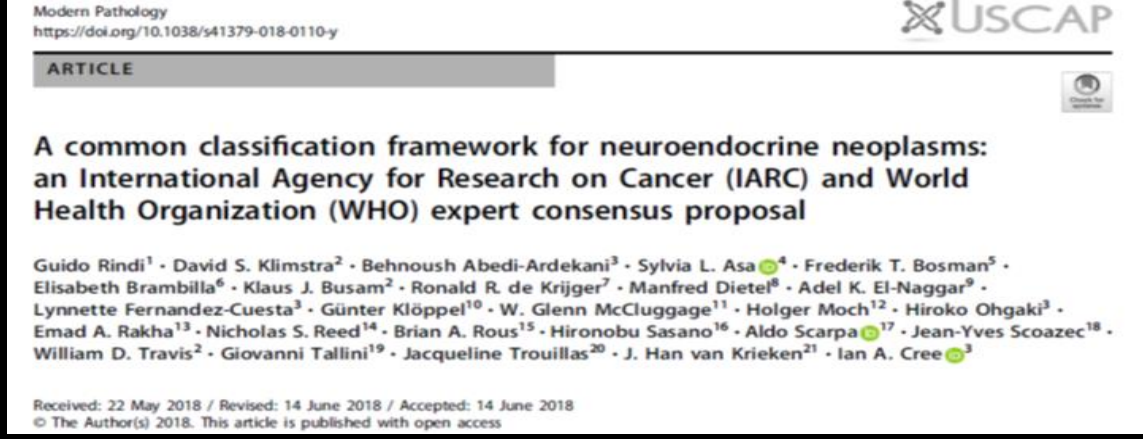
Current WHO definitions (ie: site-specific tumor definitions) should be maintained until potentially revised within each WHO Blue Book

General Considerations



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Current WHO definitions (ie: site-specific tumor definitions) should be maintained until potentially revised within each WHO Blue Book

Novel uniform standard classification terminology for NEN

(NEN-WHO 2018)

should be appended in brackets when it differs from the currently employed site-specific terminology

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		Neuroendocrine carcinoma (NEC)	Small cell lung carcinoma (Pulmonary NEC, small cell-type)[b]		Small cell lung carcinoma
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Uterus (corpus and cervix)	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Uterine neuroendocrine tumor (NET)	G1 G2 G3	Carcinoid Atypical carcinoid Atypical carcinoid
		Neuroendocrine carcinoma (NEC)	Uterine NEC, small cell-type		Small cell carcinoma
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Pancreas	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Pancreatic neuroendocrine tumor (NET)	G1 G2 G3	PanNET G1 PanNET G2 PanNET G3
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Six Tiers:

1. Site
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Six Tiers:

1. Site
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NEN – Neuroendocrine neoplasm

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Six Tiers:

1. Site
2. Category
3. Family

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Six Tiers:

1. Site
2. Category
3. Family

Either:

NEC (neuroendocrine carcinoma)

Or

NET (neuroendocrine tumour)

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Six Tiers:

1. Site
2. Category
3. Family
4. Type

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4. Type

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Represents the diagnostic entities within the families.

for some (eg: Panc NET) it is the same family

for others it subclassifies –eg: small cell vs large cell NEC

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Six Tiers:

1. Site
2. Category
3. Family
4. Type
5. Grade

Standard mitotic rate and Ki67 index

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Standard mitotic rate (per mm^2 not hpf) and Ki67 index

Presence or absence of necrosis (*punctate* or *geographic*)

Grade is site specific (eg: lung), but the parameters used for grading must be explicitly reported

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Specific Notes:

MiNEN

Not covered, NEN component is normally NEC

Non-NECs following treatment

Small cell de-differentiation in lung cancer after EGFR inhibition

Paneth-like features of treated prostate adenocarcinoma

Well differentiated neuroendocrine cell nests in rectal carcinomas following neoadjuvant treatment

Paraganglioma are mentioned in passing but not the focus of this paper

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Box 1 Some research needs identified by the expert group to illustrate the studies required to advance understanding of NEN

- General: Further genetic studies of NEN are required in many sites, ideally with computational pathology and phenotypic data on outcome. What are the common genetic and genomic features (and the differences) of NEN from different organs?
- General: Computational pathology studies of Ki-67 proliferation, and mitotic count per mm^2, are required to assess whether grade is a continuous or categorical variable, including validation against microscope counting (including inter-laboratory and observer reproducibility studies). What thresholds should be applied in clinical practice to separate grades?
- General: What is the prevalence and clinical significance of tumor heterogeneity for mitotic counts and K-67 proliferation index in NEN?
- General: Do NET and NEC occur in all anatomical sites?
- General: What are the distinguishing genetic features of NEC and NET?
- General: What is the nature of mixed neuroendocrine:non-NETs of all organs?
- General: Coordination of NEN databases is required to allow ease of data comparison between NEN arising at different sites.
- Lung: Studies on the separation between typical carcinoid and atypical carcinoid, and between these entities, SCLC and LCNEC using molecular, histological and protein expression methods. Does a G3 category of lung NET exist comparable to that in the pancreas?
- Pituitary: Studies of the genetics of NET (adenoma/NET, aggressive NET, and carcinoma) are required. It is as yet uncertain if NEC exist at this site.
- Metastases: What are the optimal diagnostic criteria and terminology to be used for metastatic rather than primary NEN?

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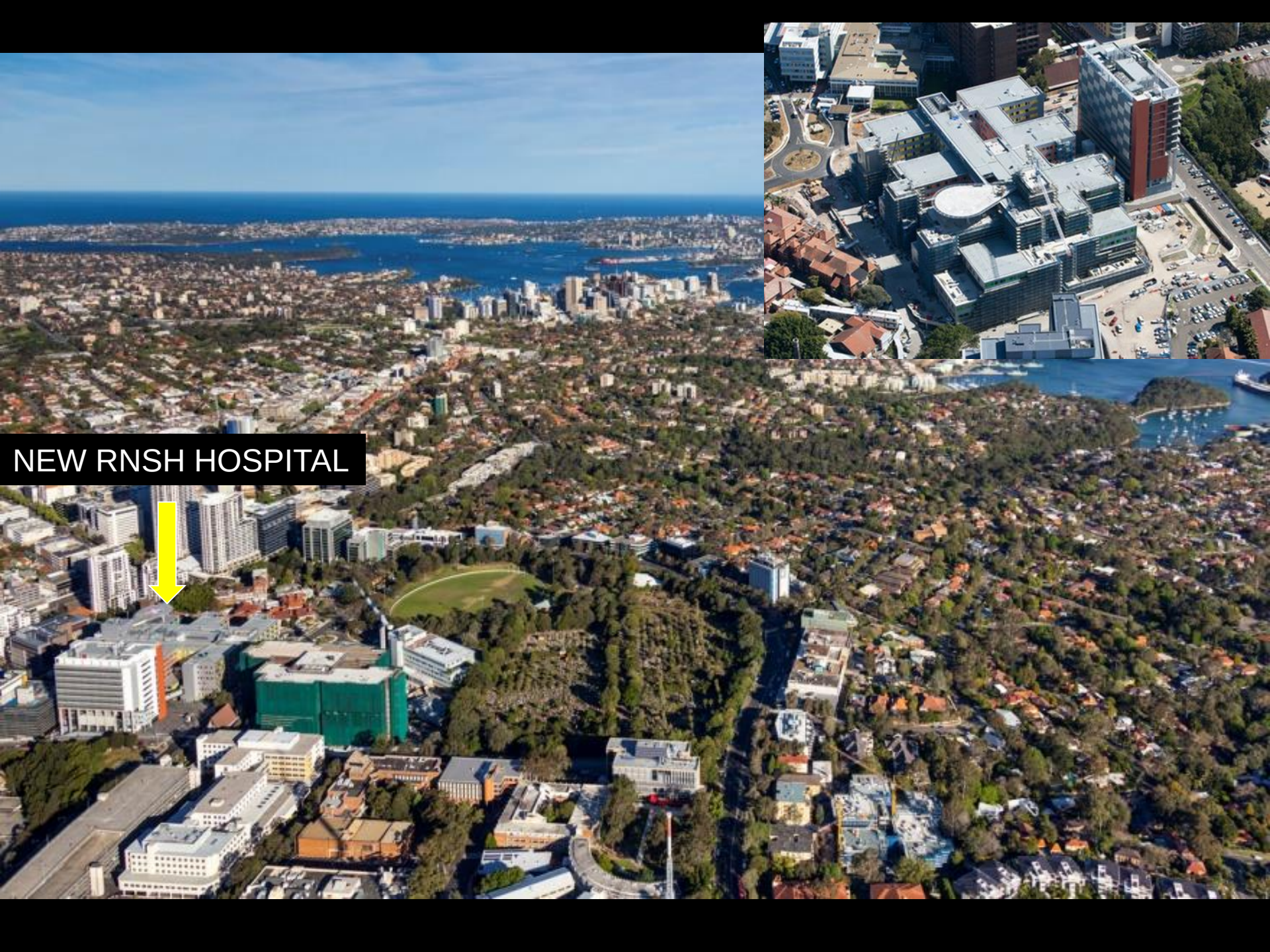
??WHO 2018/19 Grading System for NETs

TABLE 1

World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index*|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20 %	>20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC)	>20 %	>20/10 HPF
Small cell type		
Large cell type		
Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)		

* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.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